PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 221/14, A61K 31/473, C07D 209/48, A61K 31/4035, A61P 25/28

A1

(11) International Publication Number: WO 00/69829

(43) International Publication Date: 23 November 2000 (23.11.00)

(21) International Application Number: PCT/CA00/00542

(22) International Filing Date: 11 May 2000 (11.05.00)

(30) Priority Data:
60/134,578 17 May 1999 (17.05.99) US

(71) Applicant *(for all designated States except US)*: QUEEN'S UNIVERSITY [CA/CA]; Kingston, Ontario K7L 3N6 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ROSS, Gregory, M. [CA/CA]; 1090 Caitlin Crescent, Kingston, Ontario K7P 2S4 (CA). SHAMOVSKY, Igor, L. [CA/CA]; 553 Quail Court, Kingston, Ontario K7M 8Z4 (CA). MARONE, Sandra [CA/CA]; 3–234 Victoria Street, Kingston, Ontario K7L 3Y8 (CA). WEAVER, Donald, F. [CA/CA]; 27 Collegeview Crescent, Kingston, Ontario K7M 7J8 (CA). RIOPELLE, Richard, J. [CA/CA]; 32 Lakeshore Boulevard, Kingston, Ontario K7M 4J6 (CA).

(74) Agent: MBM & CO.; P.O. Box 809, Station B, Ottawa, Ontario KIP 5P9 (CA).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD OF INHIBITING NEUROTROPHIN–RECEPTOR BINDING

(57) Abstract

The present invention relates to compositions which inhibit the binding of nerve growth factor to the $p75^{NTR}$ common neurotrophin receptor and methods of use thereof. In one embodiment, the compound which inhibits binding of nerve growth factor to $p75^{NTR}$ comprises, particularly when bound to nerve growth factor, at least two of the following: (1) a first electronegative atom or functional group positioned to interact with Lys^{34} of nerve growth factor; (2) a second electronegative atom or functional group positioned to interact with Lys^{95} of nerve growth factor; (3) a third electronegative atom or functional group positioned to interact with Lys^{88} of nerve growth factor; (4) a fourth electronegative atom or functional group positioned to interact with Lys^{32} of nerve growth factor; and (5) a hydrophobic moiety which interacts with the hydrophobic region formed by Ile^{31}, Phe^{101} and Phe^{86} of nerve growth factor.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

METHOD OF INHIBITING NEUROTROPHIN-RECEPTOR BINDING

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No.: 60/134,578, filed May 17, 1999, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

The neurotrophins are a family of structurally and functionally related proteins, including Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin-3 (NT-3), Neurotrophin-4/5 (NT-4/5) and Neurotrophin-6 (NT-6). These proteins promote the survival and differentiation of diverse neuronal populations in both the peripheral and central nervous systems (Hefti, 1986; Hefti and Weiner, 1986; Levi-Montalcini, 1987; Barde, 1989; Leibrock *et al.*, 1989; Maisonpierre *et al.*, 1990; Rosenthal *et al.*, 1990; Hohn *et al.*, 1990; Gotz *et al.*, 1994; Maness *et al.*, 1994) and are involved in the pathogenesis of diverse neurological disorders. Neurotrophins exert many of their biological effects through specific interactions with a class of transmembrane receptor tyrosine kinases (trkA, trkB and trkC) (Kaplan *et al.*, 1991; Klein *et al.*, 1991, 1992; Soppet *et al.*, 1991; Squinto *et al.*, 1991; Berkemeier *et al.*, 1991; Escandon *et al.*, 1993; Lamballe *et al.*, 1991). Specificity of neurotrophin action results from their selective interactions with the trk receptors. That is, trkA only binds NGF (Kaplan *et al.*, 1991; Klein *et al.*, 1991); trkB binds BDNF and NT-4/5 (Soppet *et al.*, 1991; Squinto *et al.*, 1991; Berkemeier *et al.*, 1991; Escandon *et al.*, 1993; Lamballe *et al.*, 1991; Klein *et al.*, 1992; Vale and Shooter, 1985; Barbacid, 1993); and trkC exclusively binds NT-3 (Lamballe *et al.*, 1991; Vale and Shooter, 1985). This is particularly evident when the trk receptors are coexpressed with the common neurotrophin receptor $p75^{NTR}$. (For review see Meakin and Shooter, 1992; Barbacid, 1993; Chao, 1994; Bradshaw *et al.*, 1994; Ibáñez, 1995).

The common neurotrophin receptor $p75^{NTR}$ is a transmembrane glycoprotein structurally related to the tumor necrosis factor and CD-40 receptors (Meakin and

Shooter, 1992; Rydén and Ibáñez, 1996). As all neurotrophins bind to $p75^{NTR}$ with similar affinity (Rodriguez-Tébar *et al.*, 1990; Hallböök *et al.*, 1991; Rodriguez-Tébar *et al.*, 1992; Ibáñez, 1995), neurotrophin specificity is conventionally thought to be caused by the binding selectivity for trk receptors which are differentially expressed in different neuronal populations (Ibáñez, 1995). However, accumulated experimental data on neurotrophin activity reveal important functional aspects of $p75^{NTR}$ (Heldin *et al.*, 1989; Jing *et al.*, 1992; Herrmann, 1993; Barker and Shooter, 1994; Dobrowsky *et al.*, 1994, Matsumoto *et al.*, 1995; Marchetti *et al.*, 1996; Washiyama *et al.*, 1996). The common neurotrophin receptor enhances functions and increases binding specificity of trk receptors (Barker and Shooter, 1994; Mahadeo *et al.*, 1994; Chao and Hempstead, 1995; Rydén and Ibáñez, 1996). In addition, $p75^{NTR}$ possesses unique, trk-independent signaling properties which involve ceramide production through activation of the sphingomyelin cycle (Dobrowsky *et al.*, 1994), apoptosis (cell death) (Van der Zee *et al.*, 1996; Cassacia-Bonnefil *et al.*, 1996; Frade *et al.*, 1996), and activation of the transcription factor NFκB (Carter *et al.*, 1996). Recently, $p75^{NTR}$ has been demonstrated to participate in human melanoma progression (Herrmann *et al.*, 1993; Marchetti *et al.*, 1996). Furthermore, NGF and NT-3 increase the production of heparin by 70W melanoma cells, which is associated with their metastatic potential (Marchetti *et al.*, 1996). Although this effect has been shown to be mediated by the common neurotrophin receptor, neither BDNF nor NT-4/5 appeared to be active.

Due to the implication of NGF/$p75^{NTR}$ binding in various disease states, a need exists for pharmaceutical agents and methods of use thereof for interfering with the binding of NGF to the $p75^{NTR}$ common neurotrophin receptor.

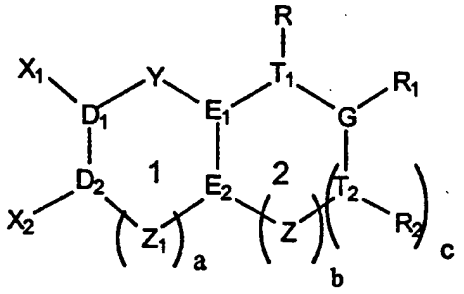
SUMMARY OF THE INVENTION

The present invention relates to the discovery of molecular structural features which contribute to the ability of a compound to inhibit the binding of NGF to the common neurotrophin receptor $p75^{NTR}$. Compounds which have these features are of use, for example, for inhibiting binding of NGF to $p75^{NTR}$. Such compounds can also be used to treat a patient having a condition which is mediated, at least in part, by the binding of NGF to $p75^{NTR}$.

In one embodiment, the present invention relates to compositions which inhibit the binding of nerve growth factor to the $p75^{NTR}$ common neurotrophin receptor and methods of use thereof.

In one embodiment, the compound which inhibits binding of nerve growth factor to $p75^{NTR}$ comprises at least two of the following: (1) a first electronegative atom or functional group positioned to interact with Lys^{34} of nerve growth factor; (2) a second electronegative atom or functional group positioned to interact with Lys^{95} of nerve growth factor; (3) a third electronegative atom or functional group positioned to interact with Lys^{88} of nerve growth factor; (4) a fourth electronegative atom or functional group positioned to interact with Lys^{32} of nerve growth factor; and (5) a hydrophobic moiety which interacts with the hydrophobic region formed by amino acid residues of nerve growth factor, including Ile^{31}, Phe^{101} and Phe^{86}. Such inhibitors, preferably, bind nerve growth factor via at least two of the foregoing interactions.

In one embodiment, compounds which inhibit binding of nerve growth factor to $p75^{NTR}$ have Formula 1,



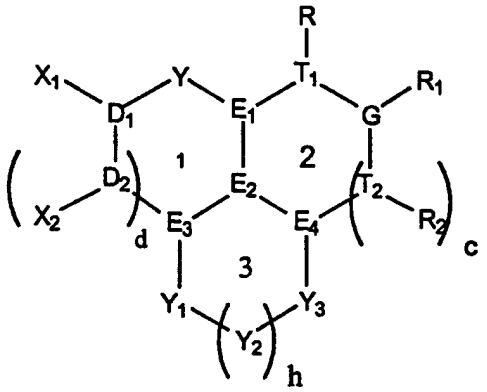
(1).

In Formula 1, D_1, D_2, E_1, E_2 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom. One of X_1 and X_2 is a hydrogen atom or absent, while the other is an electronegative atom or an electronegative functional group. R and R_2 are each, independently, an electronegative atom or an electronegative functional group, such as O, S, CH_2, or NR_3, where R_3 is H, alkyl, preferably C_1-C_6-alkyl, or aryl, such as phenyl. R, R_2 and one of X_1 and X_2 can also each be, independently, an electronegative atom or functional group, such as alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; $-PO_3H_2$; $-NO_2$;

$-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl group or a fluorine, chlorine, bromine or iodine atom. Y is N, O, S, C-L or N-L, where L is H, alkyl, preferably C_1-C_6-alkyl, or an electronegative atom or functional group, such as, but not limited to, alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; $-PO_3H_2$; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl groups or a halogen atom, such as a fluorine, chlorine, bromine or iodine atom. Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl, N-cycloalkyl and N-P, where P is a carbohydrate moiety, such as a monosaccharide group, for example, a fucosyl, glucosyl, galactosyl, mannosyl, fructosyl, gulosyl, idosyl, talosyl, allosyl, altrosyl, ribosyl, arabinosyl, xylosyl or lyxosyl group. T_1 and T_2 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom. a, b, and c are each 0 or 1, provided that at least one of b and c is 1. R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamino or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups.

It will be appreciated that in this and the following structures, the lines connecting the variables can be single or double bonds. In addition, hydrogen atoms are added to the variables as necessary to complete the valence of the atom.

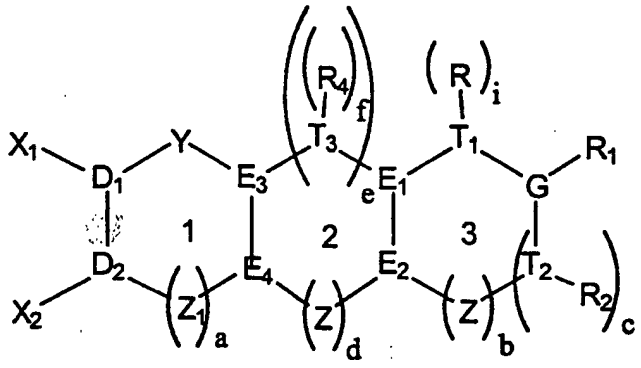
In another embodiment, the NGF/$p75^{NTR}$ binding inhibitor has Formula 3



(3)

where D_1, D_2, X_1, X_2, Y, E_1, E_2, T_1, T_2, R, G, R_1, R_2, and c have the meanings given above for these variables in Formula 1. Y_1, Y_2, and Y_3 are independently selected from the identities given for Y in Formula 1. E_3 and E_4 are each, independently, an sp^2- hybridized carbon or nitrogen atom, and d and h are, independently, 0 or 1.

In another embodiment, compounds which inhibit the binding of nerve growth facor to $p75^{NTR}$ have Formula 2,

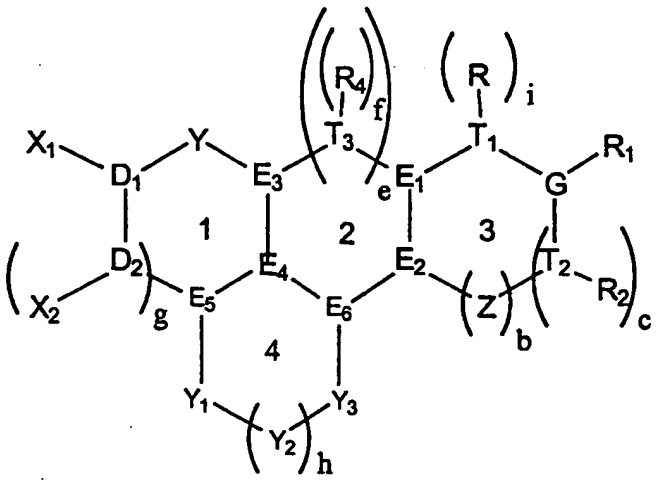


(2).

In Formula 2, D_1, D_2, E_1, E_2 , E_3, E_4 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom. One of X_1 and X_2 is a hydrogen atom or absent, while the other is an electronegative atom or an electronegative functional group. R, R_2 and R_4 are each, independently, an electronegative atom or an electronegative functional group, such as O, S, CH_2, or NR_3, where R_3 is H, OH, alkyl, preferably C_1-C_6-alkyl, or aryl, such as phenyl. R, R_2 and one of X_1 and X_2 can also each be, independently, an electronegative atom or functional group, such as alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; -CO_2H; -SO_3H; -SO_2H; -PO_3H_2; -NO_2; -ONO_2, -CNO, -SH, -CNS, -OSO_3H, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl group or a fluorine, chlorine, bromine or iodine atom. Y is N, O, S, C-L or N-L, where L is H, alkyl, preferably C_1-C_6-alkyl, or an electronegative atom or functional group, such as, but not limited to, alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; -CO_2H; -SO_3H; -SO_2H; -PO_3H_2; -NO_2; -ONO_2, -CNO, -SH, -CNS, -OSO_3H, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl groups or a halogen atom, such as a fluorine, chlorine, bromine or iodine atom. Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl, N-cycloalkyl and N-P, where P is a carbohydrate moiety, such as a monosaccharide group, for example, a fucosyl,

glucosyl, galactosyl, mannosyl, fructosyl, gulosyl, idosyl, talosyl, allosyl, altrosyl, ribosyl, arabinosyl, xylosyl or lyxosyl group. T_1, T_2 and T_3 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom. When f is 0, T_3 can further have the meanings given for Z and Z_1, above. a, b, c, d, e, f, g, h and i are each 0 or 1, provided that at least one of b and c is 1, at least one of d and e is 1 and at least one of f and i is 1. R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamine or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups.

In another embodiment, a compound which inhibits the binding of NGF to $p75^{NTR}$ has Formula 5,



wherein D_1, D_2, X_1, X_2, E_1, E_2, E_3, T_1, T_2, T_3, Z, G, R, R_1, R_2, R_4, b, e, f, i, and c have the meanings given for these variables in Formula 2. Y_1, Y_2, and Y_3 are independently selected from the identities given for Y in Formula 2, and h is 0 or 1. E_5 and E_6 are each, independently, an sp^2- hybridized carbon or nitrogen atom, and g is 0 or 1. Ring 4 can be further unsubstituted or substituted with one or more substituents, such as alkyl or aryl groups.

In another embodiment, the invention provides a pharmaceutical composition comprising at least one compound of the invention, or pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or excipient.

The invention also provides a method of inhibiting the binding of nerve growth factor to the $p75^{NTR}$ receptor. The method comprises contacting cells which express the $p75^{NTR}$ receptor with a nerve growth factor/$p75^{NTR}$ binding inhibitor of the invention in an amount which is sufficient to inhibit binding of nerve growth factor to the $p75^{NTR}$ receptor. The method can be practiced *in vivo* or *in vitro*.

In another embodiment, the invention relates to a method of treating a condition in a patient which is mediated by the binding of nerve growth factor to the $p75^{NTR}$ receptor. The method comprises administering to the patient a therapeutically effective amount of a nerve growth factor/$p75^{NTR}$ binding inhibitor of the invention. Preferably, the compound to be administered selectively inhibits the binding of nerve growth factor to $p75^{NTR}$ in cells which do not express the NGF receptor trkA.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates examples of suitable configurations for electronegative atoms in the NGF/$p75^{NTR}$ binding inhibitors of the invention.

Figure 2 illustrates examples of electronegative functional groups.

Figure 3 sets forth a synthetic pathway for certain compounds of the invention; Pg = protecting group.

Figure 4 sets forth a synthetic pathway for certain compounds of the invention.

Figure 5 sets forth a synthetic pathway for certain compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Nerve growth factor (also referred to hereinafter as "NGF") is a neurotrophin implicated in the pathogenesis of Alzheimer's disease, epilepsy and pain (Ben and Represa, 1990; McKee *et al.*, 1991; Leven and Mendel, 1993; Woolf and Doubell, 1994; Rashid *et al.*, 1995; McMahon *et al.*, 1995). The binding of NGF to its receptors is determined by distinct sequences within its primary amino acid structure. While several regions of NGF participate in the NGF/trkA interaction,

mutation studies suggest that relatively few key residues, namely those located in the NGF amino and carboxyl termini, are required for high affinity binding.

NGF displays high and low affinity binding sites in sensory and sympathetic neurons and in pheochromocytoma PC12 cells (Sutter *et al.*, 1979; Landreth and Shooter, 1980; Schechter and Bothwell, 1981). The coexpression of the common neurotrophin $p75^{NTR}$ receptor with trkA is required to form the high affinity binding site (Hempstead *et al.*, 1991; Barker and Shooter, 1994; Mahadeo *et al.*, 1994; Chao and Hempstead, 1995). Several models of the trkA-$p75^{NTR}$ interaction have been proposed to explain high affinity NGF binding (Bothwell, 1991; Chao, 1992b; Chao and Hempstead, 1995; Wolf *et al.*, 1995; Ross *et al.*, 1996; Ross *et al.*, 1997). These models differ with respect to direct (conformational model) or indirect (ligand-presentation model) interaction of $p75^{NTR}$ with trkA. Direct trkA-$p75^{NTR}$ interaction is consistent with much of the existing experimental data.

The hairpin loop at residues 29-35 of NGF is responsible for recognition by $p75^{NTR}$ (Ibáñez *et al.*, 1992; Radziejewski *et al.*, 1992), while the amino and carboxyl termini are important binding determinants for recognition by the trkA receptor (Shih *et al.*, 1994; Moore and Shooter, 1975; Suter *et al.*, 1992; Burton *et al.*, 1992; Kahle *et al.*, 1992; Luo and Neet, 1992; Drinkwater *et al.*, 1993; Treanor *et al.*, 1995; Taylor *et al.*, 1991; Shamovsky *et al.*, 1998; Shamovsky *et al.*, 1999; WO 98/06048). Truncation of either the amino or carboxyl terminus of NGF produces less active NGF analogues; similarly most deletion or point mutations of the amino terminus also lead to NGF analogues with diminished activity (Shih *et al.*, 1994; Burton *et al.*, 1992, 1995; Kahle *et al.*, 1992; Drinkwater *et al.*, 1993; Treanor *et al.*, 1995; Taylor *et al.*, 1991). On the other hand, the NGFΔ2-8 (NGF with residues 2-8 removed) and NGFΔ3-9 deletion mutants are almost as active as wild type NGF (Drinkwater *et al.*, 1993). These NGF structure-activity relationships in combination with the considerable species variability (mouse, human, guinea pig and snake) of the amino acid sequence of the NGF termini (McDonald *et al.*, 1991) are of potential value in understanding the NGF/trkA interaction.

NGF exerts its biological activity as a non-covalent dimer (Treanor *et al.*, 1995; Burton *et al.*, 1995; McDonald *et al.*, 1991; Ibáñez *et al.*, 1993; Bothwell and Shooter, 1977). Two 118 residue NGF monomers are dimerized by hydrophobic

and van der Waals interactions between their three anti-parallel pairs of β-strands; consequently, the amino terminus of one NGF monomer and the carboxyl terminus of the other are spatially juxtaposed (McDonald *et al.*, 1991). Furthermore, although a dimer has 2 pairs of termini, only one pair of termini is required for trkA receptor recognition (Treanor *et al.*, 1995; Burton *et al.*, 1995).

The X-ray crystallographic 3-dimensional structure of a dimeric mouse NGF (mNGF) has been reported (McDonald *et al.*, 1991). However, within this structure, the amino terminus (residues 1-11) and the carboxyl terminus (residues 112-118) remain unresolved for both pairs of termini. High flexibility of the NGF termini makes it difficult to experimentally determine their bioactive conformations, particularly since transition metal ions commonly used in X-ray crystallography (McDonald *et al.*, 1991) have high affinity for His residues (Gregory *et al.*, 1993) which are present in the NGF amino terminus (Bradshaw *et al.*, 1994). Indeed, conformational alterations in the receptor binding domains of NGF caused by Zn^{2+} cations leading to its inactivation have been described recently (Ross *et al.*, 1997). Since the amino and carboxyl termini are crucial for NGF bioactivity as mediated via trkA and because of the significance of NGF in multiple neurologic disease processes, the determination of the biologically active conformation of these termini is an important and challenging problem for computational chemistry.

The present invention relates to the discovery of molecular structural features which contribute to the ability of a compound to inhibit the binding of NGF to the common neurotrophin receptor $p75^{NTR}$. Compounds which have these features are of use, for example, for inhibiting binding of NGF to $p75^{NTR}$. Such compounds can also be used to treat a patient having a condition which is mediated, at least in part, by the binding of NGF to $p75^{NTR}$.

Certain compounds which inhibit the binding of NGF to $p75^{NTR}$ are disclosed in copending U.S. patent application, serial no. 09/292,450, incorporated herein by reference in its entirety.

In one embodiment, the present invention provides compounds which inhibit the binding of nerve growth factor (NGF) to the $p75^{NTR}$ receptor. The compounds have at least two of the following characteristics: (1) a first electronegative atom or functional group positioned to interact with Lys^{34} of NGF; (2) a second

electronegative atom or functional group positioned to interact with Lys^{95} of NGF; (3) a third electronegative atom positioned to interact with Lys^{88} of NGF; (4) a fourth electronegative atom or functional group positioned to interact with Lys^{32} of NGF; and (5) a hydrophobic moiety which interacts with the hydrophobic region formed by Ile^{31}, Phe^{101} and Phe^{86} of NGF. A compound having two or more of these structural attributes is referred to herein as an "NGF/$p75^{NTR}$ binding inhibitor". Preferably, the NGF/$p75^{NTR}$ binding inhibitor has at least three of the foregoing attributes when bound to NGF, more preferably at least four such attributes. Most preferably, the NGF/$p75^{NTR}$ binding inhibitor has each of the five foregoing attributes. Typically, an NGF/$p75^{NTR}$ binding inhibitor of the invention interacts with NGF via at least two of the foregoing interactions when bound to NGF.

The term "electronegative atom", as used herein, refers to an atom which carries a partial or full negative charge in a particular compound under physiological conditions. The electronegative atom can be, for example, an oxygen atom, a nitrogen atom, a sulfur atom or a halogen atom, such as a fluorine, chlorine, bromine or iodine atom. Preferably the electronegative atom is an oxygen atom. The term "electronegative functional group", as used herein, refers to a functional group which includes at least one electronegative atom. Electronegative groups include acid functional groups and other polar functional groups. For example, suitable electronegative functional groups include, but are not limited to, carbonyl, thiocarbonyl, ester, imino, amido, carboxylic acid, sulfonic acid, sulfinic acid, sulfamic acid, phosphonic acid, boronic acid, sulfate ester, hydroxyl, mercapto, cyano, cyanate, thiocyanate, isocyanate, isothiocyanate, carbonate, nitrate and nitro groups. It is to be understood that, unless otherwise indicated, reference herein to an acidic functional group also encompasses salts of that functional group in combination with a suitable cation.

An electronegative atom of the NGF/$p75^{NTR}$ binding inhibitor bears a full or partial negative charge under physiological conditions and can, therefore, interact electrostatically with the positively charged side chain of an NGF lysine residue. This will be an interaction, such as, for example, a hydrogen bond, an ion/ion interaction, an ion/dipole interaction or a dipole/dipole interaction. The hydrophobic region or moiety of the NGF/$p75^{NTR}$ binding inhibitor can interact with a

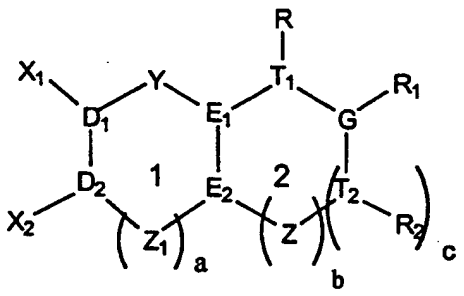
hydrophobic region of NGF via a hydrophobic interaction. Without being bound by theory, it is believed that compounds having the disclosed structural features can interact with NGF in such a way as to interfere with, and thereby inhibit, the binding of NGF to $p75^{NTR}$.

The ability of a compound to interact with the amino acid residues of NGF specified above can be determined using a structural model of NGF obtained using a energy-minimization algorithm, as described in published PCT application WO 98/06048, incorporated herein by reference in its entirety. For example, a molecule will interact with the specified residues of NGF, as discussed above, if it has at least 3 electronegative atoms (A, B and C) such that at least one of the following two conditions is satisfied: (i) atoms A and B are separated by 5-7 covalent bonds, B and C are separated by 6-8 covalent bonds, and A and C are separated by 10-14 covalent bonds and (ii) distance between A and B is between 4.5 and 7.5 angstroms, and distance between B and C is between 4.5 and 7.5 angstroms. See Figure 1. The number of covalent bonds separating atoms can be determined from the structural formula of a molecule. Distance between atoms can be determined experimentally (e.g., by X-ray crystallography or NMR spectroscopy) or evaluated theoretically using any molecular builder (e.g., SYBYL from Tripos Inc. (St. Louis, MO, USA) or QUANTA from Molecular Simulations Inc.(San Diego, CA, USA) as well as any molecular modeling technique (e.g., AMBER from Oxford Molecular Group Inc. /University of California, San Francisco or CHARMm from Molecular Simulations Inc.) or quantum chemical technique (e.g., MNDO from Oxford Molecular Group Inc. (Campbell, CA, USA) /University of Zurich; AMPAC from Semichem (Kansas City, MO, USA); CADPAC from Oxford Molecular Group Inc./Cambridge University; Gaussian-98 from Gaussian Inc. (Carnegie, PA, USA); or GAMESS from Iowa State University). Examples of suitable configurations of groups A, B and C are illustrated in Figure 1, while a representative group of electronegative functional groups is shown in Figure 2.

Preferred NGF/$p75^{NTR}$ inhibitors of the invention comprise a molecular scaffold or framework, to which the electronegative atoms or functional groups are attached, either directly or via an intervening moiety. The scaffold can be, for example, a cyclic or polycyclic moiety, such as a monocyclic, bicyclic or tricyclic

moiety, and can include one or more hydrocarbyl or heterocyclic rings. Preferably, the scaffold includes two or more fused, planar, five- or six-membered rings. The molecular scaffold presents the attached electronegative atoms, electronegative functional groups or a combination thereof, in the proper configuration or orientation for interaction with the appropriate residues of NGF. In addition, the molecular scaffold, such as polycyclic system, or a portion thereof, can serve as the hydrophobic group which interacts with hydrophobic residues of NGF, as described above.

In one embodiment, the NGF/p75^{NTR} inhibitor is of general Formula 1,



(1)

In Formula 1, D_1, D_2, E_1, E_2 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom. One of X_1 and X_2 is a hydrogen atom or absent, while the other is an electronegative atom or an electronegative functional group. R and R_2 are each, independently, an electronegative atom or an electronegative functional group, such as O, S, CH_2, or NR_3, where R_3 is H, alkyl, preferably C_1-C_6-alkyl, or aryl, such as phenyl. R, R_2 and one of X_1 and X_2 can also each be, independently, an electronegative atom or functional group, such as alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; -CO_2H; -SO_3H; -SO_2H; -PO_3H_2; -NO_2; -ONO_2, -CNO, -SH, -CNS, -OSO_3H, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl group or a fluorine, chlorine, bromine or iodine atom. Y is N, O, S, C-L or N-L, where L is H, alkyl, preferably C_1-C_6-alkyl, or an electronegative atom or functional group, such as, but not limited to, alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; -CO_2H; -SO_3H; -SO_2H; -PO_3H_2; -NO_2; -ONO_2, -CNO, -SH, -CNS, -OSO_3H, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl groups or a halogen atom, such as a fluorine, chlorine, bromine or iodine atom. Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl,

N-cycloalkyl and N-P, where P is a carbohydrate moiety, such as a monosaccharide group, for example, a fucosyl, glucosyl, galactosyl, mannosyl, fructosyl, gulosyl, idosyl, talosyl, allosyl, altrosyl, ribosyl, arabinosyl, xylosyl or lyxosyl group. T_1 and T_2 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom. a, b and c are each 0 or 1, provided that at least one of b and c is 1.

R_1 is a monocyclic or polycyclic aryl or heteroaryl, mono- or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamino or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups. Preferred monosaccharide groups include fucosyl, glucosyl, galactosyl, mannosyl, fructosyl, gulosyl, idosyl, talosyl, allosyl, altrosyl, ribosyl, arabinosyl, xylosyl and lyxosyl groups. The electronegative substituent can be bonded to the aryl or heteroaryl ring system, alkyl, cycloalkyl, or oligo- or monosaccharide group either directly or indirectly via a bridging group, for example, an alkylene group such as a C_1-C_4-alkylene group or an oxaalkylene group. Suitable directly bonded and alkylene bridged electronegative atoms and functional groups include, but are not limited to, alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; $-PO_3H_2$; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$; -OC(O)(OH); carboxyalkyl, nitroalkyl, N,N-dialkylaminosulfonyl, aminocarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, cyanocarbonylalkyl, haloalkyl, such as fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl or trichloromethyl; alkyamido or a halogen atom, such as a fluorine, chlorine, bromine or iodine atom. In one embodiment, R_1 is selected from the group consisting of groups including, but not limited to, $-(CH_2)_aCOOH$; $-(CH_2)_aNO_2$; $-(CH_2)_aOH$; $-(CH_2)_aPO_3H_2$; $-(CH_2)_aSO_3H$; $-(CH_2)_aSO_2H$; $-R_4(CH_2)_aCOOH$; $-R_4(CH_2)_aNO_2$; $-R_4(CH_2)_aPO_3H_2$; $-R_4(CH_2)_aSO_2H$; $-R_4(CH_2)_aSO_3H$; and $-R_4(CH_2)_aOH$, where a is 1 to 12, preferably 1 to about 4, and R_4 is NH or O.

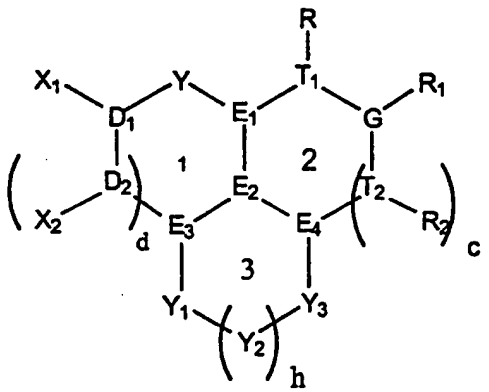
Rings 1 and 2 are each, independently, a five- or six-membered ring and, preferably, are both planar.

It is to be understood that compounds of Formula 1 and Formulas 2, 3 and 5, below, will further include double bonds between adjacent atoms as required to satisfy the valence of each atom. That is, double bonds are added to provide the

following number of total bonds to each of the following types of atoms: carbon: four bonds; nitrogen: 3 bonds; oxygen: two bonds; and sulfur: two bonds.

The term "alkyl", as used herein, refers to a normal, branched or cyclic aliphatic hydrocarbyl group, which can be saturated or partially unsaturated. Preferred alkyl groups are normal, branched and cyclic C_1-C_8-alkyl and -alkenyl groups.

In another embodiment, the NGF/p75^{NTR} binding inhibitor of Formula 3



(3)

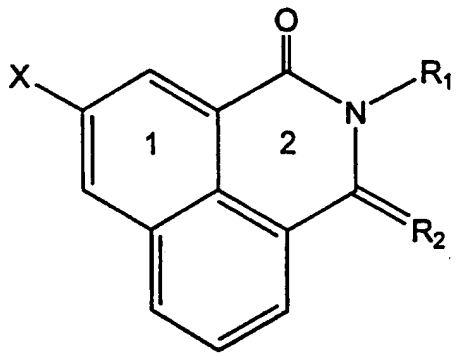
where D_1, D_2, X_1, X_2, Y, E_1, E_2, T_1, T_2, R, G, R_1, R_2, and c have the meanings given above for these variables in Formula 1. Y_1, Y_2, and Y_3 are independently selected from the identities given for Y in Formula 1. E_3 and E_4 are each, independently, an sp^2- hybridized carbon or nitrogen atom, and d and h are each, independently, 0 or 1.

In one embodiment of the compounds of Formula 3, R_1 is a mono- or polycyclic aryl or heteroaryl, oligo- or monosaccharide group which is substituted with at least one electronegative atom or electronegative group. The mono- or polycyclic aryl or heteroaryl group is preferably substituted with an acid functional group, such as alkyl-CO_2H; alkyl-SO_3H; alkyl-SO_2H; alkyl-PO_3H_2; alkyl-OSO_3H; where the alkyl group is preferably a C_1-C_4-alkyl group. In another embodiment, the electronegative atom or electronegative functional group is selected from the group consisting of alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; -CN; -NO_2; -ONO_2, -CNO, -SH, -CNS, nitroalkyl, N,N-dialkylaminosulfonyl, aminocarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, cyanocarbonylalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, acetamido and halogen atoms. R_1 can also be an alkylamino, alkyl or alkoxy group

which is substituted with at least one electronegative atom or functional group. For example, in one embodiment, R_1 is selected from the group consisting of $-(CH_2)_aNO_2$; $-(CH_2)_aOH$; $-(CH_2)_aPO_3H_2$; $-(CH_2)_aSO_3H$; $-(CH_2)_aSO_2H$; $-O(CH_2)_aCOOH$; $-O(CH_2)_aNO_2$; $-O(CH_2)_aPO_3H_2$; $-O(CH_2)_aSO_2H$; $-O(CH_2)_aSO_3H$; $-O(CH_2)_aOH$; $-NH(CH_2)_aCOOH$; $-NH(CH_2)_aNO_2$; $-NH(CH_2)_aPO_3H_2$; $-NH(CH_2)_aSO_2H$; -and $NH(CH_2)_aSO_3H$; where a is 1 to 12, preferably 1 to about 4.

In another embodiment of the compounds of Formula 3, R_1 is a phenyl group which is substituted by p-toluenesulfonamido or hydroxyl; or R_1 is a $-NH(CH_2)_aOH$ group, where a is 1 to about 4; a carboxyalkyl group, for example, a linear or branched carboxy-C_1-C_8-alkyl group; an alkoxycarbonyl group, such as a linear or branched C_1-C_8-alkoxycarbonyl group or an alkylcarbonate group, such as a linear or branched C_1-C_8-alkylcarbonate group. In this embodiment, ring atom is an sp2-hybridized carbon atom, except for G, which is a nitrogen atom; R and R_2 are both O; and d, c and h are each 1.

Preferred compounds of Formula 3 are of the formula

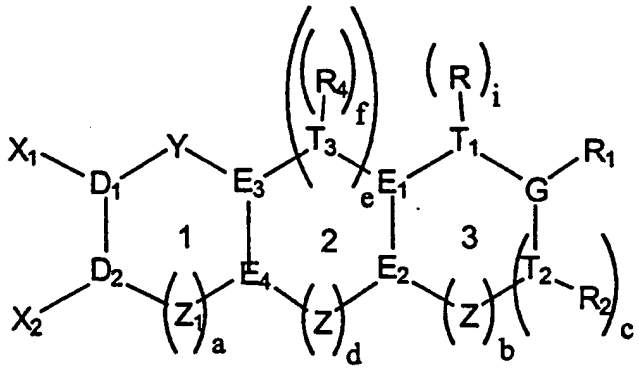


(4)

where X and R_1 have the meanings given above for these variables in Formula 1, R_2 is O, CH_2 or NR_3, where R_3 is H, alkyl, preferably C_1-C_6-alkyl, or aryl, and rings 1 and 2 can, optionally, independently be further substituted. Suitable substituents include alkyl groups, preferably normal or branched C_1-C_6-alkyl groups and halogen atoms.

In another embodiment, the NGF/p75^{NTR} binding inhibitor is of Formula 2,

(2).

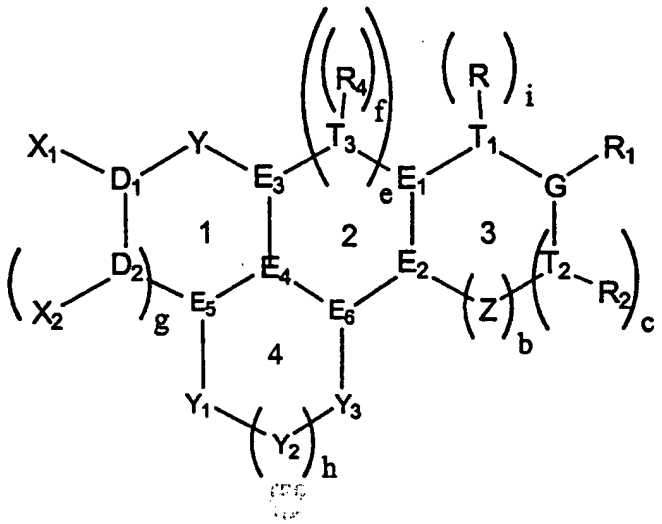


In Formula 2, D_1, D_2, E_1, E_2 , E_3, E_4 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom. One of X_1 and X_2 is a hydrogen atom or absent, while the other is an electronegative atom or an electronegative functional group. R, R_2 and R_4 are each, independently, an electronegative atom or an electronegative functional group, such as O, S, CH_2, or NR_3, where R_3 is H, alkyl, preferably C_1-C_6-alkyl, or aryl, such as phenyl. R, R_2 and one of X_1 and X_2 can also each be, independently, an electronegative atom or functional group, such as alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; -CO_2H; -SO_3H; -SO_2H; -PO_3H_2; -NO_2; -ONO_2, -CNO, -SH, -CNS, -OSO_3H, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl group or a fluorine, chlorine, bromine or iodine atom. Y is N, O, S, C-L or N-L, where L is H, alkyl, preferably C_1-C_6-alkyl, or an electronegative atom or functional group, such as, but not limited to, alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; -CO_2H; -SO_3H; -SO_2H; -PO_3H_2; -NO_2; -ONO_2, -CNO, -SH, -CNS, -OSO_3H, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl groups or a halogen atom, such as a fluorine, chlorine, bromine or iodine atom. Z and Z_1 are each, independently, O, S, CH, C=O, N, NH, N-alkyl, N-cycloalkyl and N-P, where P is a carbohydrate moiety, such as a monosaccharide group, for example, a fucosyl, glucosyl, galactosyl, mannosyl, fructosyl, gulosyl, idosyl, talosyl, allosyl, altrosyl, ribosyl, arabinosyl, xylosyl or lyxosyl group. T_1, T_2 and T_3 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom. When f is 0, T_3 can further have the meanings given for Z and Z_1, above. a, b, c, d, e, f and i are each 0 or 1, provided that at least one of b and c is 1; at least one of d and e is 1 and at least one of f and i is 1.

R_1 is a monocyclic or polycyclic aryl or heteroaryl, oligo- or monosaccharide, alkyl, cycloalkyl, arylalkyl alkylamino or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups. Preferred monosaccharide groups include fucosyl, glucosyl, galactosyl, mannosyl, fructosyl, gulosyl, idosyl, talosyl, allosyl, altrosyl, ribosyl, arabinosyl, xylosyl and lyxosyl groups. The electronegative substituent can be bonded to the aryl or heteroaryl ring system, or monosaccharide group either directly or indirectly via a bridging group, for example, an alkylene group such as a C_1-C_4-alkylene group or an oxaalkylene group. Suitable directly bonded and alkylene bridged electronegative atoms and functional groups include, but are not limited to, alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; $-PO_3H_2$; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$; -OC(O)(OH); carboxyalkyl, nitroalkyl, N,N-dialkylaminosulfonyl, aminocarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, cyanocarbonylalkyl, haloalkyl, such as fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl or trichloromethyl; alkyamido or a halogen atom, such as a fluorine, chlorine, bromine or iodine atom. In one embodiment, R_1 is selected from the group consisting of groups including, but not limited to, $-(CH_2)_aCOOH$; $-(CH_2)_aNO_2$; $-(CH_2)_aOH$; $-(CH_2)_aPO_3H_2$; $-(CH_2)_aSO_3H$; $-(CH_2)_aSO_2H$; $-R_4(CH_2)_aCOOH$; $-R_4(CH_2)_aNO_2$; $-R_4(CH_2)_aPO_3H_2$; $-R_4(CH_2)_aSO_2H$; $-R_4(CH_2)_aSO_3H$; and $-R_4(CH_2)_aOH$, where a is 1 to 12, preferably 1 to about 4, and R_4 is NH or O.

Rings 1, 2 and 3 are each, independently, a five-or six-membered ring and, preferably, are each planar.

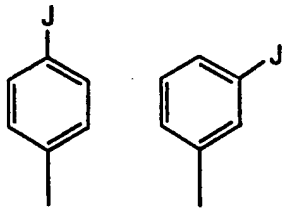
In another embodiment, the compound is of Formula 5,

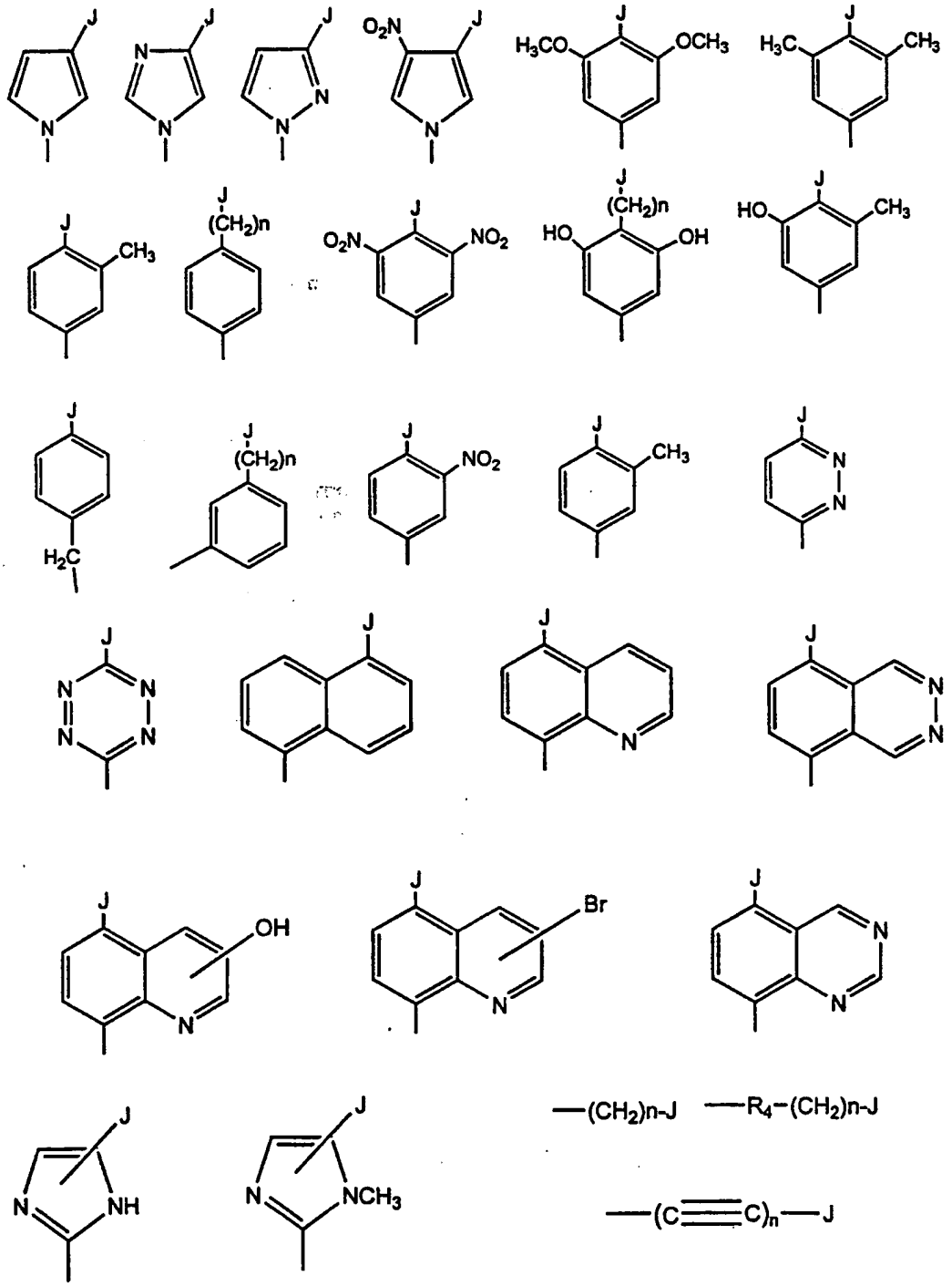


(5),

wherein D_1, D_2, X_1, X_2, E_1, E_2, E_3, T_1, T_2, T_3, Z, G, R, R_1, R_2, R_4, b, c, e, f and i have the meanings given for these variables in Formula 2. Y_1, Y_2, and Y_3 are independently selected from the identities given for Y in Formula 2, and g and h are each, independently, 0 or 1. E_5 and E_6 are each, independently, an sp^2- hybridized carbon or nitrogen atom, and g is 0 or 1. Ring 4 can be further unsubstituted or substituted with one or more substituents, such as alkyl or aryl groups.

In one embodiment of the compounds of Formulas 1, 2, 3 and 5, R_1 is selected from the group consisting of substituted phenylene, naphthylene, quinolylene and other substituted aromatic and heteroaromatic groups. R_1 can also be a substituted ethynyl or poly(ethynyl) group. Suitable identities for R_1 include, but are not limited to, the groups shown below.

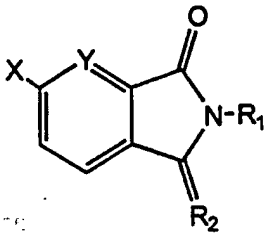




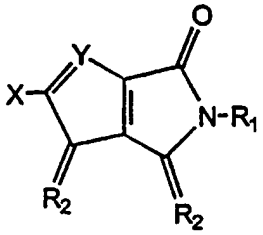
In each of these groups, J can be any of the electronegative atoms or groups described in the definition of R_1 in Formulas 1 and 2. Preferably, J is selected from the group consisting of -OH, -CN, $-NO_2$, $-CO_2H$, $-SO_3H$, $-SO_2H$, -F, -Cl, -Br, -I,

$-PO_3H_2$, $-CF_3$, $-SO_2N(CH_3)_2$, $-C(O)NH_2$, $-C(O)CH_3$, $-C(O)OCH_3$, -C(O)CN, $-CH_2F$, $-CH_2Cl$, $-CF_2H$, $-CCl_2H$, $-CCl_3$ and $-NHC(O)CH_3$; R_4 is NH or O, and n is an integer from 0 to about 6.

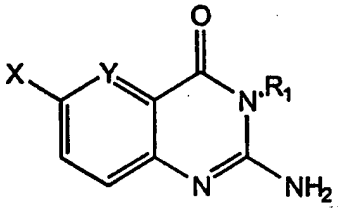
Preferred compounds of Formula 1 are represented by Formulas 6-14, 16-18, 21-30 and 32-34, below. Preferred compounds of Formula 3 are represented by Formulas 15, 19, 20 and 31 below.



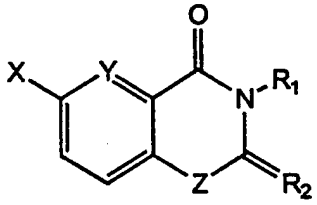
6



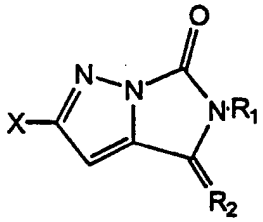
7



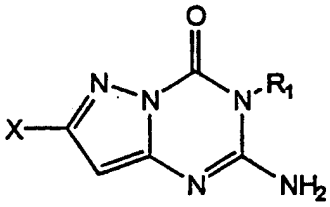
8



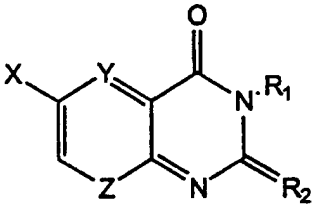
9



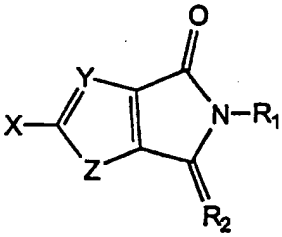
10



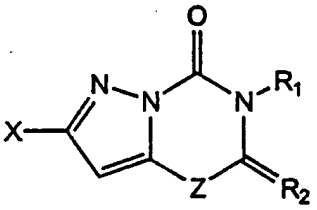
11



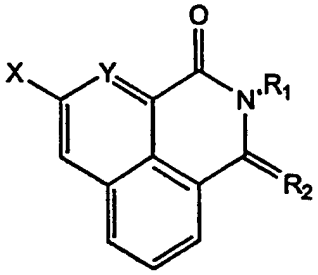
12

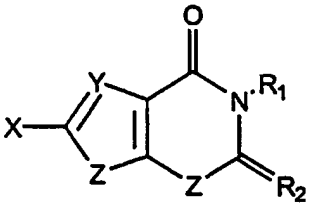


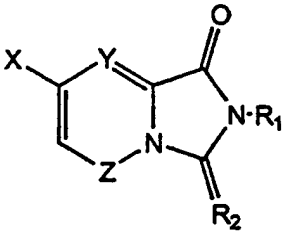
13



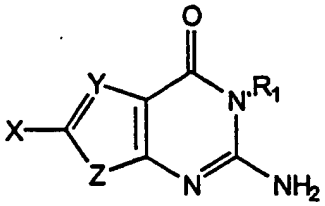
14

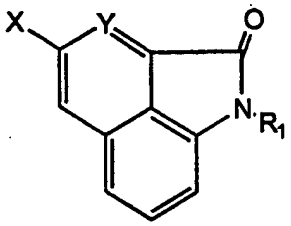


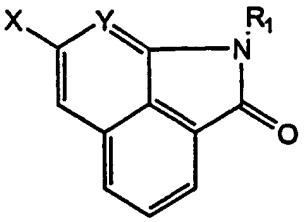




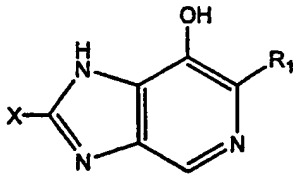
15 16 17

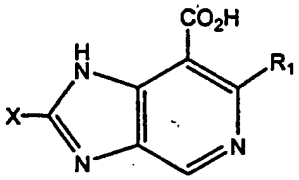


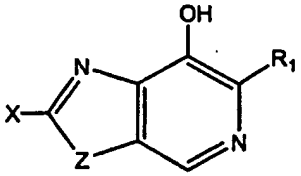




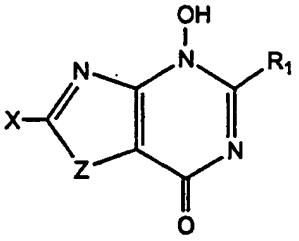
18 19 20

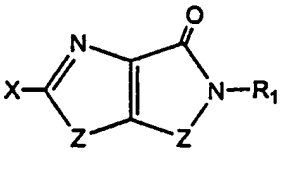


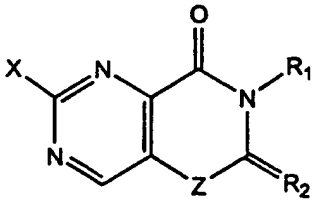




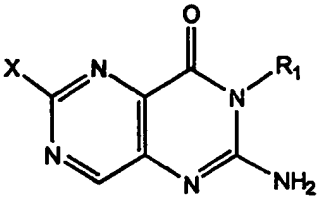
21 22 23

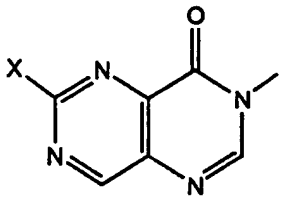


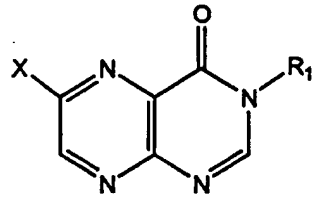




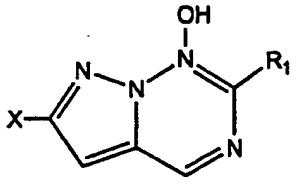
24 25 26



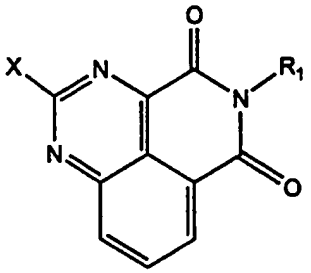




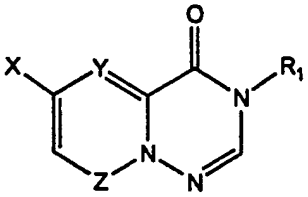
27 28 29



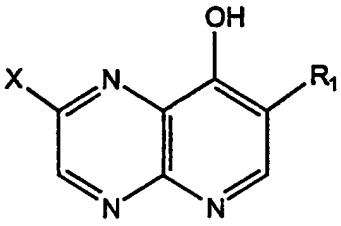
30



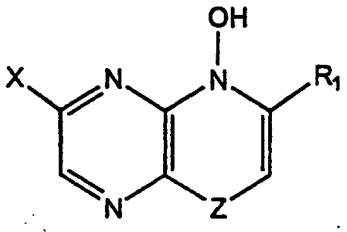
31



32



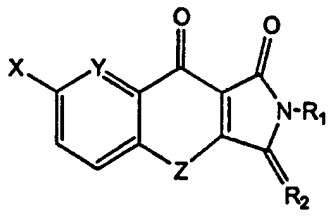
33



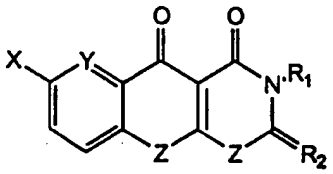
34

In each of Formulas 6-34, R_1, X and Y have the meanings given above for these variables in Formula 1. In Formulas 6, and 9-15, Z is selected from the group consisting of O, S, NH, N-alkyl, N-cycloalkyl and N-P, wherein P is a carbohydrate moiety, preferably a monosaccharide moiety, such as a fucosyl, glucosyl, galactosyl, mannosyl, fructosyl, gulosyl, idosyl, talosyl, allosyl, altrosyl, ribosyl, arabinosyl, xylosyl or lyxosyl group. In Formulas 6, 7, 9, 10 and 12-17, R_2 is selected from the group consisting of O, S, CH_2 and NR_3, wherein R_3 is H, OH, aryl or alkyl.

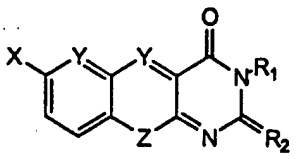
Preferred compounds of Formulas 2 and 5 are of Formulas 35-49 below.



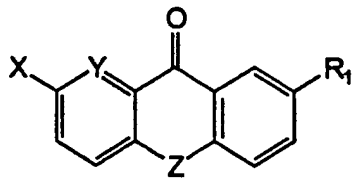
35

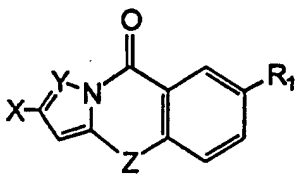


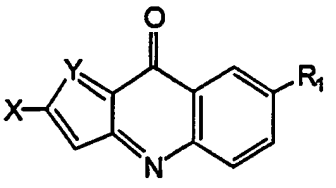
36



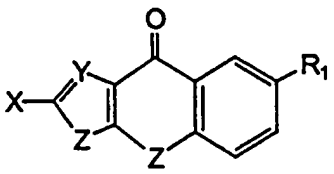
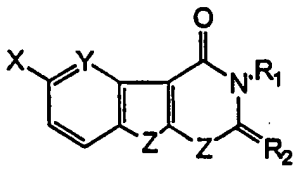
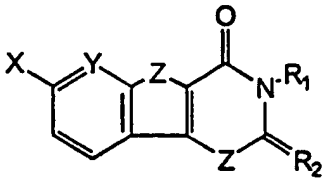
37



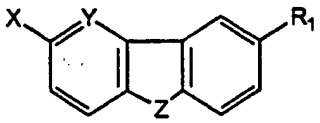
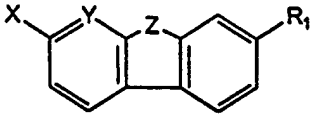
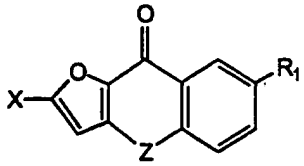




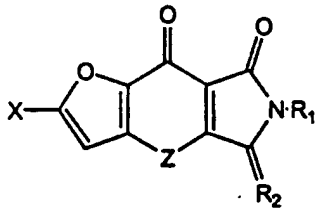
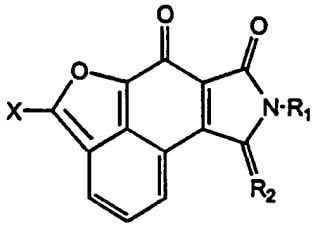
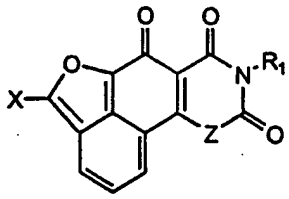
38 39 40

41 42 43

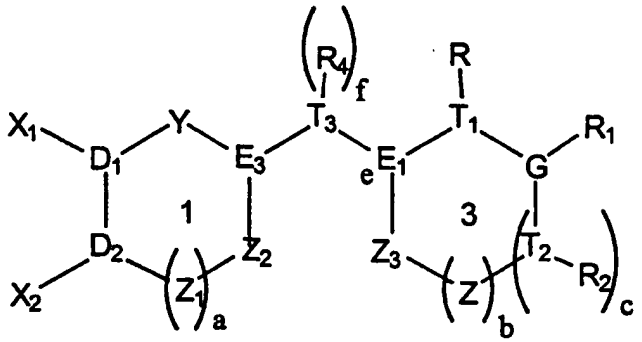
44 45 46

47 48 49

In Formulas 32-46, the structural variables X, R_1, R_2, Z and Y each have the identities given previously for Formula 2.

In another embodiment, the NGF/$p75^{NTR}$ binding inhibitor is of general formula 50,

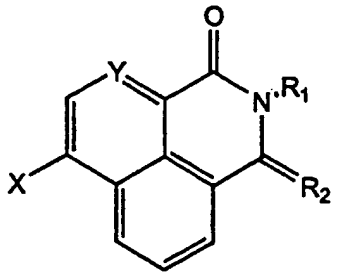


(50).

In Formula 50, the structural variables D_1, D_2, X_1, X_2, E_1, E_2, E_3, T_1, T_2, T_3, Z, G, R, R_1, R_2, R_4, b,and c have the meanings given for these variables in Formula 2. T_3 is

an sp^2- or sp^3-hybridized carbon or nitrogen atom, and is preferably an sp^2-hybridized carbon or nitrogen atom.

A preferred subset of compounds of Formula 3 is represented by Formula 51,

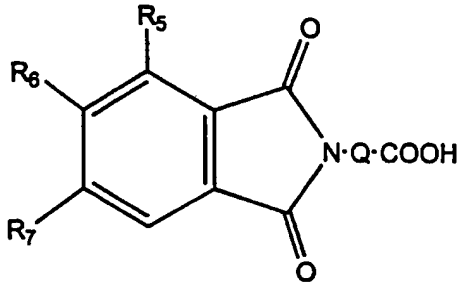


(51).

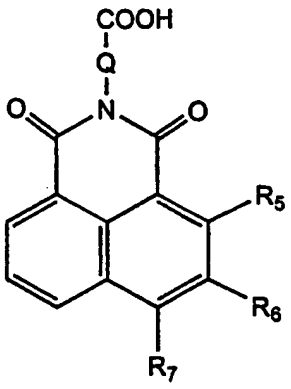
In Formula 51, X, Y and R_1 each have the meanings given for these variables in Formula 1. R_2 is O, S, CH_2 or N-R_3, wherein R_3 is H, OH, alkyl, preferably normal or branched C_1-C_6-alkyl, or aryl, such as phenyl or substituted phenyl.

In a preferred embodiment, the NGF/$p75^{NTR}$ inhibitor exhibits greater NGF/$p75^{NTR}$ binding inhibition in cells which express $p75^{NTR}$ but not trkA than in cells which express both $p75^{NTR}$ and trkA. The binding of NGF to $p75^{NTR}$ in cells which do not express trkA can, under certain conditions, mediate apoptotic cell death. The $p75^{NTR}$ receptor has a greater affinity for NGF in this proapoptotic state, that is, in cells which do not express trkA. Compounds which exhibit greater NGF/$p75^{NTR}$ binding inhibition in the absence of trkA advantageously selectively inhibit or interfere with processes such as apoptotic cell death, while having a smaller effect on other $p75^{NTR}$-mediated processes.

Preferred compounds which selectively inhibit the binding of NGF to $p75^{NTR}$ in cells which do not express trkA include compounds of Formulas 52 and 53, below.



52



53

In Formulas 52 and 53, Q is selected from the group consisting of C_1-C_5-alkylene; para- and meta-phenylene; cycloalkylene, carbohydrate and para- and meta- $-CH_2C_6H_4-$. In Formulas 51 and 52, R_5, R_6 and R_7 are, preferably, each, independently, H, -COOH or $-NO_2$. More preferably, two of R_5, R_6 and R_7 are H and the other is -COOH or $-NO_2$.

The present invention also relates to a method of inhibiting the binding of NGF to $p75^{NTR}$. The method comprises contacting NGF in the presence of $p75^{NTR}$ with an NGF/$p75^{NTR}$ binding inhibitory amount of a NGF/$p75^{NTR}$ inhibitor compound, thereby inhibiting binding of NGF to $p75^{NTR}$. The method can be practiced *in vitro*, for example, in a cell culture screening assay to screen compounds which potentially bind, activate or inhibit receptor function.. In such a method, the inhibitor compound can function by binding and eliminating any competing function of NGF in the sample or culture. The inhibitor compounds can also be used to control NGF activity in neuronal cell culture. The method can also be practised *in vivo*, for example, to inhibit one or more processes mediated by binding of NGF to $p75^{NTR}$.

In another embodiment, the invention provides a method of treating a condition mediated by NGF/$p75^{NTR}$ binding in a patient. The method comprises the step of administering to the patient a therapeutically effective amount of a NGF/$p75^{NTR}$ binding inhibitor, such as any of the inhibitors described above. The condition to be treated can be any condition which is mediated, at least in part, by binding of NGF to the $p75^{NTR}$ receptor. Such conditions include, but are not limited

to, Alzheimer's disease, epilepsy, pain, multiple sclerosis, amyotrophic lateral sclerosis, stroke and cerebral ischemia.

Preferably, the NGF/$p75^{NTR}$ binding inhibitor to be administered selectively inhibits the binding of NGF to $p75^{NTR}$ in cells which do not express trkA. In this embodiment, the condition is mediated, at least in part, by the binding of NGF to the $p75^{NTR}$ receptor in cells which do not express the trkA receptor. Generally, such conditions are mediated by NGF-induced apoptotic cell death.

The quantity of a given compound to be administered will be determined on an individual basis and will be determined, at least in part, by consideration of the individual's size, the severity of symptoms to be treated and the result sought. The NGF/$p75^{NTR}$ binding inhibitor can be administered alone or in a pharmaceutical composition comprising the inhibitor, an acceptable carrier or diluent and, optionally, one or more additional drugs.

The NGF/$p75^{NTR}$ binding inhibitor can be administered subcutaneously, intravenously, parenterally, intraperitoneally, intradermally, intramuscularly, topically, enteral (e.g., orally), rectally, nasally, buccally, sublingually, vaginally, by inhalation spray, by drug pump or via an implanted reservoir in dosage formulations containing conventional non-toxic, physiologically acceptable carriers or vehicles. The preferred method of administration is by oral delivery. The form in which it is administered (e.g., syrup, elixir, capsule, tablet, solution, foams, emulsion, gel, sol) will depend in part on the route by which it is administered. For example, for mucosal (e.g., oral mucosa, rectal, intestinal mucosa, bronchial mucosa) administration, nose drops, aerosols, inhalants, nebulizers, eye drops or suppositories can be used. The compounds and agents of this invention can be administered together with other biologically active agents, such as analgesics, anti-inflammatory agents, anesthetics and other agents which can control one or more symptoms or causes of a $p75^{NTR}$-mediated condition.

In a specific embodiment, it may be desirable to administer the agents of the invention locally to a localized area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, transdermal patches, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous,

or gelatinous material, including membranes, such as sialastic membranes or fibers. For example, the agent can be injected into the joints.

The compound of the invention can, optionally, be administered in combination with one or more additional drugs which, for example, are known for treating and/or alleviating symptoms of the condition mediated by $p75^{NTR}$. The additional drug can be administered simultaneously with the compound of the invention, or sequentially.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically (or prophylactically) effective amount of one or more NGF/$p75^{NTR}$ binding inhibitors, preferably one or more compounds of Formulas 1, 2, 4 or 5, as described above, and a pharmaceutically acceptable carrier or excipient. Suitable pharmaceutically acceptable carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (e.g., NaCl), alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, cyclodextrin, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, etc. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrollidone, sodium saccharine, cellulose, magnesium carbonate, etc.

The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachet indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The pharmaceutical compositions of the invention can also include an agent which controls release of the NGF/$p75^{NTR}$ inhibitor compound, thereby providing a timed or sustained relase composition.

The present invention also relates to prodrugs of the NGF/$p75^{NTR}$ binding inhibitors disclosed herein, as well as pharmaceutical compositions comprising such prodrugs. For example, compounds of the invention which include acid functional groups or hydroxyl groups can also be prepared and administered as a corresponding ester with a suitable alcohol or acid. The ester can then be cleaved by endogenous enzymes within the patient to produce the active agent.

In a further embodiment, the invention relates to the use of an NGF/$p75^{NTR}$ binding inhibitor, such as any of the compounds described above, for treating a condition mediated by binding of NGF to $p75^{NTR}$. The invention further relates to the use of these compounds for the manufacture of a medicament for treating a condition mediated by binding of NGF to $p75^{NTR}$.

Representative syntheses of compounds of the invention are set forth in the following examples. Other synthetic pathways that can be used to prepare certain compounds of the invention are illustrated in Figures 3 and 4.

EXAMPLES

Example 1 Synthesis of NGF/p75^{NTR} inhibitors

General methods

Reagents and solvents were obtained from commercial sources (Sigma, Aldrich, BDH). THF was dried by refluxing with benzophenone and potassium and subsequently distilled. All other solvents were utilized as they were received.

Thin layer chromatography (TLC) solvent systems used are given in Table 1. These were developed by ascending TLC on precoated aluminum backed sheets of silica gel 60 F254 (Merck). TLC plates were developed using ultra-violet light, iodine crystal and/or ninhydrin.

Melting points (mp) were determined on a Thomas Hoover Unimelt melting point apparatus and are uncorrected.

NMR spectra of final compounds were determined on an AVANCE 300 MHz NMR spectrometer. All NMR samples were prepared in DMSO-d6 unless otherwise indicated. Chemical shifts are reported as δ parts per million using DMSO as an internal reference. Mass spectrometric (MS) analyses are performed on a Varian Instrument VG Quattro multiple quadripole spectrometer using electrospray ionization (ESI). The spectra were all obtained in the negative ion mode. IR spectra were recorded on a Bomen MB-120 FT-IR spectrophotometer.

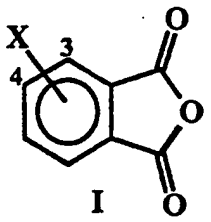
Abbreviations used herein are: HOAc , glacial acetic acid; THF, tetrahydrofuran; DMSO-d_6, deuterated dimethylsulfoxide; $CHCl_3$, chloroform: MeCN, acetonitrile; H_2O, distilled water; MeOH, methanol; EtOH, ethanol; TEA, triethylamine; EtOAc, ethyl acetate.

Table 1: List of Solvent Systems.

Solvent Code	Solvent System	Solvent Ratio
A	MeOH:HOAc	5:1
B	MeCN:H_2O:MeOH	8:1:1
C	MeCN:H_2O:MeOH	4:1:1
D	$CHCl_3$:MeOH:HOAc	95:10:3
E	EtOH:HOAc	50:1

General Synthesis of Phthalimide derivatives

Method A: The phthalimide series of compounds was prepared through the condensation of stoichiometric amounts of phthalic anhydride or a phthalic anhydride derivative (I) with an appropriate primary amine (II). The combined reagents were dissolved in glacial acetic acid, placed under a N_2 atmosphere and refluxed. The progress of the reaction was monitored by TLC. Final clear solutions were concentrated *in vacuo* and the resulting crude material was either reprecipitated from 1,4-dioxane/1N HCl or HOAc/H_2O and/or recrystallized from 95% ethanol, THF or 1,4-dioxane. In the instances where the final product precipitated out of the reaction solution, the completed reaction mixture was cooled to room temperature, the solid collected by filtration and washed with distilled water. This precipitate was reprecipitated with 1,4-dioxane/ 1N HCl or HOAc/H_2O and/or recrystallized from 95% ethanol, THF or 1,4-dioxane.



I

$H_2N—R_1$

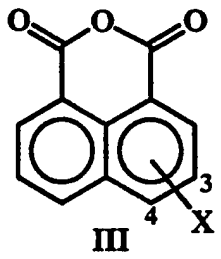
II

where X and R_1 are as previously defined.

Method B: Reaction conditions and purification procedures were similar to those of method A. However, instead of stoichiometric amounts of reagents, the anhydride (I) and the primary amine(II) were combined in a 1:2 ratio with the optional addition of 1 equivalent of anhydrous sodium acetate. During the course of preparing the various phthalimide derivatives, these reaction conditions were found to lead to increased product yields.

General Synthesis of Naphthalimide derivatives

Method A: 1,8-naphthalic anhydride or its derivative (III) was reacted with an appropriate primary amine (II) under conditions similar to those of method A for the phthalimide series. Glacial acetic acid, dry THF, dry 1,4-dioxane or DMSO were used as solvents. Purification also included fractional recrystallisation.



III

H_2N-R_1

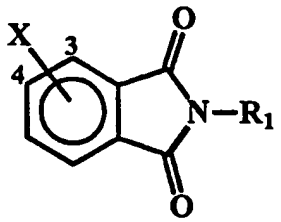
II

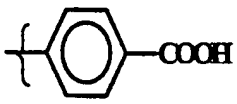
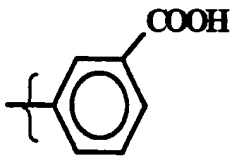
Method B: As per method B for the phthalimide series. Glacial acetic acid was the only solvent used under these conditions.

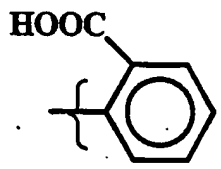
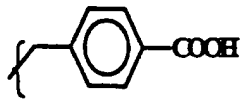
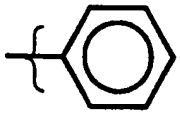
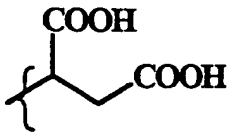
General Synthesis of Amino Phthalimide or Amino Naphthalimide Derivatives

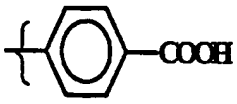
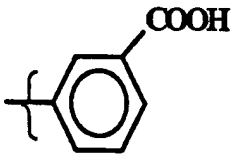
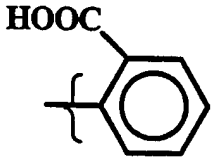
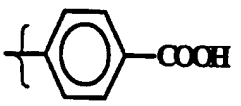
The amino-N-substituted phthalimides and amino-N-substituted naphthalimides were synthesized *via* the reduction of the corresponding nitro-N-substituted phthalimides or nitro-N-substituted naphthalimides with 10% palladium on activated charcoal in glacial acetic acid or glacial acetic acid/1,4-dioxane under a hydrogen atmosphere. Upon completion, as indicated by TLC, the catalyst was removed by filtering through a celite pad and the clear filtrate concentrated. The crude material was purified using procedures similar to those described above.

Table 2: Synthesized Phthalimide Derivatives



Compd.	X	R_1	Name
100	4-COOH	CH_2COOH	4-carboxy-N-(1-carboxymethyl)phthalimide
101	4-COOH	CH_2CH_2COOH	4-carboxy-N-(2-carboxyethyl)phthalimide
102	4-COOH	$CH_2(CH_2)_2COOH$	4-carboxy-N-(3-carboxypropyl)phthalimide
103	4-COOH	$CH_2(CH_2)_3COOH$	4-carboxy-N-(4-carboxybutyl)phthalimide
104	4-COOH	$CH_2(CH_2)_4COOH$	4-carboxy-N-(5-carboxypentyl)phthalimide
105	4-COOH		4-carboxy-N-(*p*-carboxyphenyl)phthalimide
106	4-COOH		4-carboxy-N-(*m*-carboxyphenyl)phthalimide

Compd.	X	R_1	Name
107	4-COOH		4-carboxy-N-(*o*-carboxyphenyl)phthalimide
108	4-COOH		4-carboxy-N-(*p*-carboxyphenylmethyl)phthalimide
109	4-COOH		4-carboxy-N-phenylphthalimide
111	4-COOH		4-carboxy-N-aspartylphthalimide
120	3-NO_2	CH_2COOH	3-nitro-N-(1-carboxymethyl)phthalimide
121	3-NO_2	CH_2CH_2COOH	3-nitro-N-(2-carboxyethyl)phthalimide
122	3-NO_2	$CH_2(CH_2)_2COOH$	3-nitro-N-(3-carboxypropyl)phthalimide
123	3-NO_2	$CH_2(CH_2)_3COOH$	3-nitro-N-(4-carboxybutyl)phthalimide
124	3-NO_2	$CH_2(CH_2)_4COOH$	3-nitro-N-(5-carboxypentyl)phthalimide

Compd.	X	R_1	Name
125	3-NO_2		3-nitro-N-(*p*-carboxyphenyl)phthalimide
126	3-NO_2		3-nitro-N-(*m*-carboxyphenyl)phthalimide
127	3-NO_2		3-nitro-N-(*o*-carboxyphenyl)phthalimide
140	4-NO_2	CH_2COOH	4-nitro-N-(1-carboxymethyl)phthalimide
141	4-NO_2	CH_2CH_2COOH	4-nitro-N-(2-carboxyethyl)phthalimide
142	4-NO_2	$CH_2(CH_2)_2COOH$	4-nitro-N-(3-carboxypropyl)phthalimide
143	4-NO_2	$CH_2(CH_2)_3COOH$	4-nitro-N-(4-carboxybutyl)phthalimide
144	4-NO_2	$CH_2(CH_2)_4COOH$	4-nitro-N-(5-carboxypentyl)phthalimide
145	4-NO_2		4-nitro-N-(*p*-carboxyphenyl)phthalimide

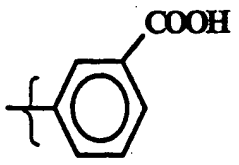
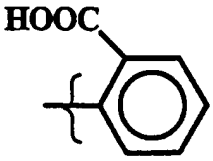
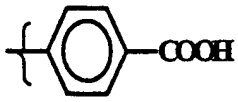
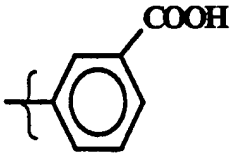
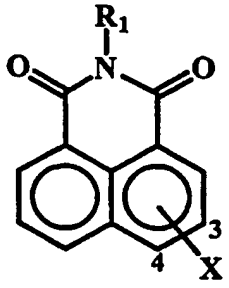
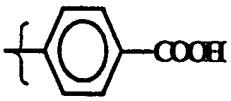
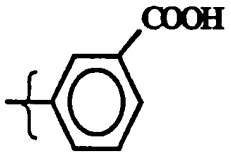
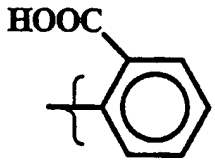
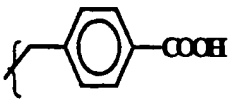
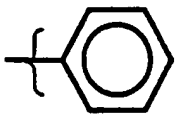
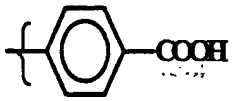
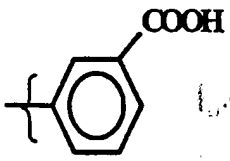
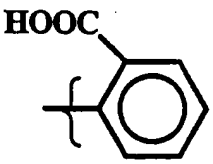
Compd.	X	R_1	Name
146	4-NO_2		4-nitro-N-(*m*-carboxyphenyl)phthalimide
147	4-NO_2		4-nitro-N-(*o*-carboxyphenyl)phthalimide
165	4-NH_2		4-amino-N-(*p*-carboxyphenyl)phthalimide
166	4-NH_2		4-amino-N-(*m*-carboxyphenyl)phthalimide

Table 3: Synthesized Naphthalimide Derivatives



Compd.	X	R_1	Name
205	3-NO_2		3-nitro-N-(*p*-carboxyphenyl)-1,8-naphthalimide
206	3-NO_2		3-nitro-N-(*m*-carboxyphenyl)-1,8-naphthalimide
207	3-NO_2		3-nitro-N-(*o*-carboxyphenyl)-1,8-naphthalimide
208	3-NO_2		3-nitro-N-(*p*-carboxyphenylmethyl)-1,8-naphthalimide

Compd.	X	R_1	Name
209	3-NO_2		3-nitro-N-phenyl-1,8-naphthalimide
225	4-NO_2		4-nitro-N-(*p*-carboxyphenyl)-1,8-naphthalimide
226	4-NO_2		4-nitro-N-(*m*-carboxyphenyl)-1,8-naphthalimide
227	4-NO_2		4-nitro-N-(*o*-carboxyphenyl)-1,8-naphthalimide

Synthesis of Phthalimide Derivatives:

Method A:

4-carboxy-N-(carboxymethyl)phthalimide (100)

4-carboxyphthalic anhydride (benzene tricarboxylic acid anhydride) (1.0 g, 0.0052 mol), glycine (0.3907 g, 0.0052 mol) and 50-60 mls of glacial acetic acid were added to a 100 ml round-bottom flask equipped with a reflux condenser, heating mantle and stir plate. The system was placed under a N_2 atmosphere and heated to a gentle reflux. The progress of the reaction was monitored by TLC. After 7 hours the clear colourless solution was cooled to room temperature. The resulting white precipitate was filtered through a Buchner funnel and washed three times with 10 mls of distilled water. This crude material was recrystallized in EtOH/H_2O to

afford the desired product as a powdery white solid. The filtrate was evaporated under vacuum using a rotary evaporator. The crude material was recrystallized from EtOH/H_2O to yield a second batch of white powdery product. Individual batches were dried in air for 24 hours and then *in vacuo* for 48-72 hours to afford 100 in a combined yield of 1.02 g (78%): mp=262-265°C; R_f 0.70 (A): R_f 0.47 (B): R_f 0.20 (D): ^{1}H NMR (DMSO-d_6) δ 4.33 (s, 2H), 8.02 (d, *J*= 7.8 Hz, 1H), 8.24 (bs, 1H), 8.36 (d, *J*=7.8 Hz, 1H); MS *m/z* (rel intensity) 249 (13), 248 (100), 204 (36); IR (cm^{-1}): 2750-3300 (OH), 3052 (C=CH), 2671 (C-H), 1776 (C=O), 1731 (C=O), 1705 (C=O), 1620 (C=C), 1420 (C=C), 1300 (C-O), 1122 (C-O), 746 (C=CH).

4-carboxy-N-(2-carboxyethyl)phthalimide (101)

4-carboxyphthalic anhydride (1.0 g, 0.0052 mol) and β-alanine (0.46, 0.0052 mol) were refluxed as above for 7 hours. Crystallisation of the product from EtOH yielded 1.37 g (78%) of 101 as a white solid: mp=240-242°C; R_f 0.77 (A): R_f 0.67 (B): R_f 0.33 (D): ^{1}H NMR (DMSO-d_6); MS *m/z* (rel intensity) 263 (14), 262 (100); IR (cm^{-1}): 2800-3250 (OH), 3150 (C=CH), 2671 (C-H), 1777 (C=O), 1725 (C=O), 1705 (C=O), 1620 (C=C), 1452 (C=C), 1385(C-O), 1226 (C-O), 731 (C=CH). MS *m/z* (rel intensity) 263 (14), 262 (100).

4-carboxy-N-(3-carboxypropyl)phthalimide (102)

4-carboxyphthalic anhydride (1.0 g, 0.0052 mol) and 4-aminobutyric acid (0.54 g, 0.0052 mol) were refluxed as above for 7 hours. Crystallisation of the product from EtOH yielded 1.1 g (76%) of 102 as a white solid: mp=218-220°C; R_f 0.78 (A): R_f 0.84 (C): R_f 0.28 (D): ^{1}H NMR (DMSO-d_6); IR (cm^{-1}): 2800-3250 (OH), 3050 (C=CH), 2680 (C-H), 1760 (C=O), 1712 (bs, C=O), 1560 (C=C), 1430 (C=C), 1397 (C-O), 1305 (C-O), 727 (C=CH); MS *m/z* (rel intensity) 277 (18), 276 (100).

4-carboxy-N-(4-carboxybutyl)phthalimide (103)

4-carboxyphthalic anhydride (1.0 g, 0.0052 mol) and 5-aminopentanoic acid (0.61 g, 0.0052 mol) were refluxed as above overnight. Crystallisation of the product from EtOH yielded 1.51 g (72%) of 103 as a white solid: mp=223°C; R_f

0.79 (A): R_f 0.92 (C): R_f 0.36 (D): IR (cm^{-1}): 2750-3375 (OH), 3084 (C=CH), 2665 (C-H), 1767 (C=O), 1705 (bs, C=O), 1620 (C=C), 1486 (C=C), 1402 (CH_2), 1382 (C-O), 1302 (C-O), 732 (C=CH); MS *m/z* (rel intensity) 291 (15), 290 (100).

4-carboxy-N-(5-carboxypentyl)phthalimide (104)

4-carboxyphthalic anhydride (1.0 g, 0.0052 mol) and 6-aminohexanoic acid (0.68 g, 0.0052 mol) were refluxed as above overnight. Crystallisation of the product from EtOH yielded 1.35 g (85%) of 104 as a white solid: mp=202-204°C; R_f 0.80 (A): R_f 0.84 (B): R_f 0.47 (D): IR (cm^{-1}): 2800-3250 (OH), 3103 (C=CH), 2675 (C-H), 1769 (C=O), 1709 (bs, C=O), 1625 (C=C), 1485 (C=C), 1403(C-O), 1303 (C-O), 730 (C=CH); MS *m/z* (rel intensity) 305 (16), 304 (100).

4-carboxy-N-(*p*-carboxyphenyl)phthalimide (105)

4-carboxyphthalic anhydride (1.0 g, 0.0052 mol) and *p*-aminobenzoic acid (0.714 g, 0.0052 mol) were refluxed as above overnight. A clean product from the mother liquor fraction was not obtained. Crystallisation of the precipitated product from MeOH/$H_2$0 yielded 0.88 g (55%) of 105 as a white solid: mp=377-379°C; R_f 0.90 (A): R_f 0.76 (B): R_f 0.46 (D): IR (cm^{-1}): 2750-3200 (OH), 3077 (C=CH), 2652 (C-H), 1777 (C=O), 1731 (C=O), 1699 (C=O), 1604 (C=C), 1512 (C=C), 1485 (C=C), 1428 (C=C), 1376 (C-O), 1310 (C-O), 1092 (C-O), 723 (C=CH); MS *m/z* (rel intensity) 311 (23), 310 (100).

4-carboxy-N-(*m*-carboxyphenyl)phthalimide (106)

4-carboxyphthalic anhydride (1.0 g, 0.0052 mol) and *m*-aminobenzoic acid (0.714 g, 0.0052 mol) were refluxed as above overnight. Crystallisation of the product from MeOH yielded 1.21 g (72%) of 106 as a white solid: mp= >380°C; R_f 0.87 (A): R_f 0.75 (C): R_f 0.27 (D):IR (cm^{-1}): 2700-3125 (OH), 3090 (C=CH), 2665 (C-H), 1780 (C=O), 1731 (C=O), 1699 (C=O), 1610 (C=C), 1589 (C=C), 1484 (C=C), 1452 (C=C), 1383 (C-O), 1310 (C-O), 1222 (C-O), 722 (C=CH); MS *m/z* (rel intensity) 311 (22), 310 (100).

4-carboxy-N-(*o*-carboxyphenyl)phthalimide (107)

4-carboxyphthalic anhydride (1.0 g, 0.0052 mol) and *m*-aminobenzoic acid (0.714 g, 0.0052 mol) were refluxed as above for 24 hours. Crystallisation of the product from HOAc/H_2O yielded 0.96 g (59%) of 107 as a white solid: mp=262-264°C; R_f 0.81 (A): R_f 0.77 (B): R_f 0.28 (D): ^{1}H NMR (DMSO-d_6) δ 7.55 (dd, *J*=7.8, 1.3 Hz, 1H), 7.64 (ddd, *J*=7.8, 7.8, 1.3 Hz, 1H), 7.78 (ddd, *J*=7.8, 7.8, 1.4 Hz), 8.06 (dd, *J*=7.8, 1.4 Hz, 1H), 8.09 (dd, *J*=7.7, 0.6 Hz, 1H), 8.32 (dd, *J*=7.7, 1.3 Hz, 1H), 8.117 (dd, *J*=1.3, 0.6 Hz, 1H); IR (cm^{-1}): 2800-3100 (OH), 3064 (C=CH), 2646 (C-H), 1779 (C=O), 1716 (bs, C=O), 1602 (C=C), 1493 (C=C), 1462 (C=C), 1385 (C-O), 1261 (C-O), 1217 (C-O), 722 (C=CH); MS *m/z* (rel intensity) 311 (20), 310 (100).

4-carboxy-N-(*p*-carboxyphenyl methyl)phthalimide (108)

4-carboxyphthalic anhydride (0.5 g, 0.0026 mol) and 4-(aminomethyl)benzoic acid (0.39 g, 0.0026 mol) were refluxed as above overnight. Crystallisation of the product from 1,4-dioxane/H_2O yielded 0.67 g (79%) of 108 as a white solid: mp=365-366°C; R_f 0.76 (A): R_f 0.71 (C): R_f 0.50 (D): IR (cm^{-1}): 2800-3100 (OH), 3071 (C=CH), 2678 (C-H), 1782 (C=O), 1712 (bs, C=O), 1611 (C=C), 1577 (C=C), 1428 (C=C), 1391 (C-O), 1300 (C-O), 1105 (C-O), 734 (C=CH); MS *m/z* (rel intensity) 325 (20), 324 (100).

4-carboxy-N-aspartylphthalimide (111)

4-carboxyphthalic anhydride (0.5 g, 0.0026 mol) and L-aspartic acid (0.346 g, 0.0026 mol) were refluxed as above for 5 days. The clear colourless solution was concentrated under vacuum. The crude material was dissolved in EtOAc and extracted with water (3 X 25 ml). The EtOAc layer was dried over magnesium sulfate, concentrated under vacuum with a rotary evaporator and recrystallized in EtOAc/hexanes. The product was dried in air for 24 hours and then *in vacuo* for 48-72 hours to afford 0.15 g (19%) 111 as a powdery white solid: mp= 242-243 °C; R_f 0.76 (A): R_f 0.52 (B): R_f (D): IR (cm^{-1}): 2750-3250 (OH), 3090 (C=CH), 2639 (C-H), 1783 (C=O), 1736 (bs, C=O), 1628 (C=C), 1485 (C=C), 1389 (bs, C-O), 1298

(C-O), 1196 (C-O), 729 (C=CH); MS *m/z* (rel intensity) 307 (156), 306 (100), 262 (29), 218 (49).

3-nitro-N-(1-carboxymethyl)phthalimide (120)

3-nitrophthalic anhydride (0.5 g, 0.0026 mol) and glycine (0.19 g, 0.0026 mol) were refluxed as above overnight. The clear solution was concentrated under vacuum with a rotary evaporator and the crude material triturated with hot 1,4-dioxane. Undissolved material was filtered through a Buchner funnel and washed twice with 1 ml hot 1,4-dioxane. The filtrate was diluted with water. A white solid appeared which was filtered through a Buchner and washed three times with 3-5 ml water. The product was dried in air for a short time and then *in vacuo* for 48-72 hours to afford 0.52 g (81%) 120 as off white crystals: mp=200-202°C; R_f 0.73 (A): R_f 0.77 (C): R_f 0.23 (D): IR (cm^{-1}): 2800-3200 (OH), 3096 (C=CH), 2652 (C-H), 1779 (C=O), 1724 (C=O), 1690 (C=O), 1648 (C=C), 1544 (N=O), 1470 (C=C), 1448 (C=C), 1412 (C-O), 1368 (N=O), 1260 (C-O), 722 (C=CH); MS *m/z* (rel intensity) 250 (15), 249 (100), 205 (89).

3-nitro-N-(2-carboxyethyl)phthalimide (121)

3-nitrophthalic anhydride (0.5 g, 0.0026 mol) and β-alanine (0.23 g, 0.0026 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.55 g (80 %) 121 as a pale yellow powder: mp=146-148°C; R_f 0.73 (A): R_f 0.87 (C): R_f 0.57 (D): ^{1}H NMR (DMSO-d_6) δ 2.60 (t, *J*=7.4 Hz, 2H), 3.78 (t, *J*=7.4 Hz, 2H), 8.07 (dd, *J*=7.5, 8.0 Hz, 1H), 8.16 (d, *J*=7.5 Hz, 1H), 8.27 (d, *J*=8.0, 1H); IR (cm^{-1}): 2800-3200 (OH), 3097 (C=CH), 2620 (C-H), 1781 (C=O), 1725 (bs, C=O), 1617 (C=C), 1545 (N=O), 1468 (C=C), 1450 (C=C), 1395 (C-O), 1360 (N=O), 1235 (C-O), 723 (C=CH); MS *m/z* (rel intensity) 264 (76), 263 (100), 191 (90).

3-nitro-N-(3-carboxypropyl)phthalimide (122)

3-nitrophthalic anhydride (0.5 g, 0.0026 mol) and 4-aminobutyric acid (0.268 g, 0.0026 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.57 g (79 %) 122 as a very pale orange powder:

mp=144-146°C; R_f 0.62 (A): R_f 0.87 (C): R_f 0.78 (D): IR (cm^{-1}): 3000-3250 (OH), 3219 (C=CH), 2953 (C-H), 1778 (C=O), 1716 (C=O), 1667 (C=O), 1615 (C=C), 1548 (N=O), 1442 (C=C), 1395 (C-O), 1355 (N=O), 1189 (C-O), 723 (C=CH); MS *m/z* (rel intensity) 313 (100), 278 (65), 277 (42), 191 (71).

3-nitro-N-(4-carboxybutyl)phthalimide (123)

3-nitrophthalic anhydride (0.5 g, 0.0026 mol) and 5-aminopentanoic acid (0.30 g, 0.0026 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.55 g (73 %) 123 as pale yellow flat crystals: mp=158-160°C; R_f 0.69 (A): R_f 0.90 (C): R_f 0.73 (D): ^{1}H NMR (DMSO-d_6) δ 1.53 (m, 2H), 1.58 (m, 2H), 2.24 (t, *J*=7.1 Hz, 2H), 3.57 (t, *J*=6.7 Hz, 2H), 8.04 (dd, *J*=8.0, 7.5 Hz, 1H), 8.16 (d, *J*=7.5 Hz, 1H), 8.27 (d, *J*=8.0 Hz, 1H); IR (cm^{-1}): 2800-3130 (OH), 3096 (C=CH), 2691 (C-H), 1774 (C=O), 1723 (bs, C=O), 1616 (C=C), 1543 (N=O), 1466 (C=C), 1443 (C=C), 1396 (C-O), 1358 (N=O), 1209 (C-O), 1050 (C-O), 722 (C=CH); MS *m/z* (rel intensity) 291 (92), 247 (31), 191 (100).

3-nitro-N-(5-carboxypentyl)phthalimide (124)

3-nitrophthalic anhydride (0.5 g, 0.0026 mol) and 6-aminohexanoic acid (0.34 g, 0.0026 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.75 g (95 %) 124 as a pale yellow powder: mp=144°C; R_f 0.68 (A): R_f 0.89 (C): R_f 0.71 (D): IR (cm^{-1}): 2800-3180 (OH), 3096 (C=CH), 2620 (C-H), 1777 (C=O), 1723 (bs, C=O), 1617 (C=C), 1543 (N=O), 1468 (C=C), 1442 (C=C), 1395 (C-O), 1359 (N=O), 1057 (C-O), 723 (C=CH); MS *m/z* (rel intensity) 305 (100), 191 (17).

3-nitro-N-(*p*-carboxyphenyl)phthalimide (125)

3-nitrophthalic anhydride (0.79 g, 0.0041 mol) and *p*-aminobenzoic acid (0.56 g, 0.0041 mol) were refluxed as above overnight. Concentration of the solution under vacuum by rotary evaporator and crystallisation of the product from EtOH/H_2O yielded 1.1 g (68%) of 125 as a vibrant light yellow powder: mp=338-340°C; R_f 0.76 (A): R_f 0.89 (C): R_f 0.66 (D): IR (cm^{-1}): 2750-3125 (OH), 3091 (C=CH), 2671 (C-H), 1782 (C=O), 1736 (C=O), 1693 (C=O), 1610 (C=C), 1585

(C=C), 1529 (N=O), 1513 (C=C), 1433 (C=C), 1378 (C-O), 1360 (N=O), 1291 (C-O), 766 (C=CH); MS *m/z* (rel intensity) 311 (100), 267 (25), 191 (15).

3-nitro-N-(*m*-carboxyphenyl)phthalimide (126)

3-nitrophthalic anhydride (0.79 g, 0.0041 mol) and *m*-aminobenzoic acid (0.56 g, 0.0041 mol) were refluxed as above overnight. Concentration of the solution under vacuum by rotary evaporator and crystallisation of the product from EtOH/H_2O yielded 1.23 g (76%) of 126 as a vibrant yellow powder: mp=354-355°C; R_f 0.77 (A): R_f 0.84 (C): R_f 0.54 (D): IR (cm^{-1}): 2740-3100 (OH), 3088 (C=CH), 2665 (C-H), 1776 (C=O), 1725 (bs, C=O), 1614 (C=C), 1542 (N=O), 1460 (C=C), 1420 (C=C), 1382 (C-O), 1356 (N=O), 1120 (C-O), 717 (C=CH); MS *m/z* (rel intensity) 311 (100), 267 (65), 191 (60).

3-nitro-N-(*o*-carboxyphenyl)phthalimide (127)

3-nitrophthalic anhydride (1.0 g, 0.0052 mol) and *o*-aminobenzoic acid (0.71 g, 0.0052 mol) were refluxed as above for four days. The clear solution was purified as per 120 to yield 0.34 g (21 %) 127 as pale orange grains: mp=190-192°C; R_f 0.74 (A): R_f 0.87 (C): R_f 0.62 (E): IR (cm^{-1}): 2700-3300 (OH), 3093 (C=CH), 2620 (C-H), 1718 (C=O), 1681 (bs, C=O), 1609 (C=C), 1592 (C=O), 1534 (N=O), 1482 (C=C), 1451 (C=C), 1360 (N=O), 1316 (C-O), 1257 (C-O), 771 (C=CH) ; MS *m/z* (rel intensity) 311 (50), 285 (100), 241 (55), 122 (45).

4-nitro-N-(1-carboxymethyl)phthalimide (140)

4-nitrophthalic anhydride (0.25 g, 0.0013 mol) and glycine (0.097 g, 0.0013 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.28 g (86 %) 140 as very pale yellow crystals: mp=195-96°C; R_f 0.79 (A): R_f 0.75 (B): R_f 0.28 (D): IR (cm^{-1}): 2811-3150 (OH), 3115 (C=CH), 1787 (C=O), 1730 (bs, C=O), 1622 (C=C), 1551 (N=O), 1412 (C=C), 1391 (C-O), 1351 (N=O), 1117 (C-O), 720 (C=CH); MS *m/z* (rel intensity) 250 (7), 249 (62), 205 (100), 122 (10).

4-nitro-N-(2-carboxyethyl)phthalimide (141)

4-nitrophthalic anhydride (0.25 g, 0.0013 mol) and β-alanine (0.115 g, 0.0013 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.31 g (90 %) 141 as a very pale yellow powder: mp=206-208°C; R_f 0.84 (A): R_f 0.81 (B): R_f 0.55 (D): IR (cm^{-1}): 2800-3125 (OH), 3109 (C=CH), 2646 (C-H), 1780 (C=O), 1718 (bs, C=O), 1621 (C=C), 1536 (N=O), 1441 (C=C), 1395 (C-O), 1346 (N=O), 1228 (C-O), 724 (C=CH); MS *m/z* (rel intensity) 263 (100), 191 (36).

4-nitro-N-(3-carboxypropyl)phthalimide (142)

4-nitrophthalic anhydride (0.25 g, 0.0013 mol) and 4-aminobutyric acid (0.134 g, 0.0013 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.35 g (98 %) 142 as very pale yellow powder: mp=176-178°C; R_f 0.82 (A): R_f 0.83 (B): R_f 0.71 (D): IR (cm^{-1}): 3000-3300 (OH), 3122 (C=CH), 1775 (C=O), 1707 (bs, C=O), 1617 (C=C), 1545 (N=O), 1446 (C=C), 1399 (C-O), 1349 (N=O), 1167 (C-O), 722 (C=CH); MS *m/z* (rel intensity) 291 (100), 191(8).

4-nitro-N-(4-carboxybutyl)phthalimide (143)

4-nitrophthalic anhydride (0.25 g, 0.0013 mol) and 5-aminopentanoic acid (0.152 g, 0.0013 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.37 g (98 %) 143 as dull white crystals: mp=172°C; R_f 0.93 (A): R_f 0.83 (B): R_f 0.69 (D): ^{1}H NMR (DMSO-d_6) δ 1.83 (m, 2H), 2.29 (t, *J*=7.2 Hz, 2H), 3.64 (t, *J*=6.7 Hz, 2H), 8.01 (d, *J*=7.6 Hz, 1H), 8.45 (d, *J*=1.9 Hz, 1H), 8.59 (dd, *J*=7.6, 1.9 Hz, 1H); IR (cm^{-1}): 2750-3200 (OH), 3056 (C=CH), 2620 (C-H), 1773 (C=O), 1707 (bs, C=O), 1624 (C=C), 1543 (N=O), 1438 (C=C), 1403 (C-O), 1351 (N=O), 1217 (C-O), 1068 (C-O), 723 (C=CH); MS *m/z* (rel intensity) 305 (100).

4-nitro-N-(5-carboxypentyl)phthalimide (144)

4-nitrophthalic anhydride (0.25 g, 0.0013 mol) and 6-aminohexanoic acid (0.177 g, 0.0013 mol) were refluxed as above overnight. The clear solution was

purified as per 120 to yield 0.39 g (97 %) 144 as very pale dull orange crystals: mp=140°C; R_f 0.86 (A): R_f 0.85 (B): R_f 0.75 (D): IR (cm^{-1}): 2875-3125 (OH), 3064 (C=CH), 1775 (C=O), 1706 (bs, C=O), 1624 (C=C), 1544 (N=O), 1437 (C=C), 1398 (C-O), 1348 (N=O), 1069 (C-O), 722 (C=CH); MS *m/z* (rel intensity) 277 (100), 251 (11), 191 (124).

4-nitro-N-(*p*-carboxyphenyl)phthalimide (145)

4-nitrophthalic anhydride (0.25 g, 0.0013 mol) and *p*-aminobenzoic acid (0.18 g, 0.0013 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.33 g (81 %) 145 as a very pale dull yellow powder: mp=331-332°C; R_f 0.86 (A): R_f 0.92 (C): R_f 0.56 (D): IR (cm^{-1}): 2750-3150 (OH), 3116 (C=CH), 2684 (C-H), 1780 (C=O), 1730 (bs, C=O), 1622 (C=C), 1608 (C=C), 1543 (N=O), 1510 (C=C), 1434 (C=C), 1383 (C-O), 1350 (N=O), 1103 (C-O), 727 (C=CH); MS *m/z* (rel intensity) 311 (100), 267 (87).

4-nitro-N-(*m*-carboxyphenyl)phthalimide (146)

4-nitrophthalic anhydride (0.25 g, 0.0013 mol) and *m*-aminobenzoic acid (0.18 g, 0.0013 mol) were refluxed as above overnight. The clear solution was purified as per 120 to yield 0.30 g (74 %) 146 as a very pale dull yellow powder: mp=368-370°C; R_f 0.83 (A): R_f 0.93 (C): R_f 0.53 (D): IR (cm^{-1}): 2700-3280 (OH), 3122 (C=CH), 2687 (C-H), 1781 (C=O), 1727 (bs, C=O), 1622 (C=C), 1588 (C=C), 1546 (N=O), 1461 (C=C), 1420 (C=C), 1386 (C-O), 1350 (N=O), 1113 (C-O), 727 (C=CH); MS *m/z* (rel intensity) 311 (68), 285 (46), 267 (46), 191 (100).

4-nitro-N-(*o*-carboxyphenyl)phthalimide (147)

4-nitrophthalic anhydride (0.5g, 0.0026 mol) and *o*-aminobenzoic acid (0.36 g, 0.0026 mol) were refluxed as above for four days. The clear solution was purified as per 120 with an additional final crystallisation from acetone/H_2O to yield 0.12 g (15 %) 147 as a very pale dull yellow powder: mp=242-243 °C; R_f 0.80 (A): R_f 0.88 (C): R_f 0.49 (D): IR (cm^{-1}): 2725-3100 (OH), 3071 (C=CH), 2646 (C-H), 1786 (C=O), 1730 (C=O), 1693 (C=O), 1620 (C=C), 1601 (C=C), 1538 (N=O), 1491

(C=C), 1452 (C=C), 1383 (C-O), 1345 (N=O), 1123 (C-O), 723 (C=CH); MS *m/z* (rel intensity) 311 (33), 267 (76), 241 (54), 136 (100)..

Method B:

4-carboxy-N-phenylphthalimide (109)

4-carboxyphthalic anhydride (benzene tricarboxylic acid anhydride) (1.0 g, 0.0052 mol), aniline (0.96 g, 0.0104 mol), and 70-80 mls of glacial acetic acid were added to a 100 ml round-bottom flask equipped with a reflux condenser, heating mantle and stir plate. The system was placed under a N_2 atmosphere. A white solid precipitated out of the clear pale yellow solution within 1 minute. The mixture was heated to a gentle reflux. More precipitate formed during the course of the reaction. After 12 hours the mixture was cooled to room temperature and concentrated under vacuum with a rotary evaporator. The crude material was reprecipitated in 1,4-dioxane and IN HCl. The resultant white precipitate was filtered through a Buchner funnel and washed three times with 15 ml of water. The product was dried in air for 24 hours and then *in vacuo* for 48-72 hours to afford 1.25 g (90%) 109 as a white fluffy solid: mp=257-258°C; R_f 0.83 (A): R_f 0.76 (B): R_f 0.62 (D): IR (cm^{-1}): 2800-3125 (OH), 3071 (C=CH), 2665 (C-H), 1788 (C=O), 1719 (bs, C=O), 1602 (C=C), 1596 (C=C), 1504 (C=C), 1487 (C=C), 1399 (C-O), 1124 (C-O), 724 (C=CH); MS *m/z* (rel intensity) 267 (16), 266 (100).

Synthesis of Amino-Phthalimide Derivatives

4-amino-N-(*p*-carboxyphenyl)phthalimide (165)

4-nitro-N-(*p*-carboxyphenyl)phthalimide (145) (0.2 g, 0.6 mmol) partially dissolved in 30 ml of 1,4-dioxane and 2 ml HOAc was added to a three necked round bottom flask equipped with a rubber septum, a gas inlet adapter and an adapter tightly fitted with a balloon. After the reaction vessel was purged three times with N_2, 0.02g of 10% Pd on activated charcoal was added. The reaction vessel was then flushed three times with H_2. The heterogenous mixture was vigorously stirred under a hydrogen atmosphere overnight. The catalyst was removed by filtration through a celite pad and the filtrate concentrated under vacuum to give a bright yellow solid. The crude material which contained unreacted nitro compound was

resubjected to the above procedure. Resulting crude material was triturated with hot 1,4-dioxane and undissolved material removed by filtration. The filtrate was diluted with water. The ensuing solid was filtered through a Buchner funnel and washed three times with 1 ml water. The product was dried in air for a short time and then *in vacuo* for 48-72 hours to afford 0.071 g (39%) 165 as a dark yellow solid: mp=270-271°C; R_f 0.88 (A): R_f 0.80 (C): R_f 0.49 (D): IR (cm^{-1}): 3366 (NH), 3193 (NH), 2750-3200 (OH), 3075 (C=CH), 2669 (C-H), 1767 (C=O), 1752 (C=O), 1701 (bs, C=O), 1637 (C=C), 1607 (C=C), 1514 (C=C), 1482 (C=C), 1370 (C-N), 1220 (C-O), 740 (C=CH); MS *m/z* (rel intensity) 282 (16), 281 (100), 237 (71) 120 (43).

4-amino-N-(*m*-carboxyphenyl)phthalimide (166)

4-nitro-N-(*m*-carboxyphenyl)phthalimide (145) (0.2 g, 0.6 mmol) was catalytically hydrogenated as 165. Crystallization from 1,4-dioxane/ 1N HCl to yield 0.091g (50%) of 166 as a dark orange solid: mp=306-308°C; R_f 0.81 (A): R_f 0.79 (B): R_f 0.50 (D): ^{1}H NMR (DMSO-d_6) δ 6.57 (bs, 2H), 7.05 (d, *J*=8.0 Hz, 1H), 7.06 (d, *J*=7.2 Hz, 1H), 7.50 (dd, *J*=7.2, 8.0 Hz, 1H), 7.67 (m, 2H), 7.97 (m, 2H);IR (cm^{-1}): 3393 (NH), 3193 (NH), 2750-3125 (OH), 3082 (C=CH), 2669 (C-H), 1755 (C=O), 1707 (bs, C=O), 1643 (C=C), 1587 (C=C), 1458 (C=C), 1406 (C=C), 1372 (C-N), 1221 (C-O), 755 (C=CH); MS *m/z* (rel intensity) 317 (100) 282 (15), 281 (93), 233 (44) 161 (33).

Synthesis of Naphthalimide Derivatives:

Method A:

3-nitro-N-(*p*-carboxyphenyl)-1,8-naphthalimide (205)

3-nitro-1,8-naphthalic anhydride (0.5 g, 0.0020 mol) and *p*-aminobenzoic acid (0.28 g, 0.0020 mol) were refluxed in dry (distilled from CaH_2) 1,4-dioxane as per 100 for seven days. The dark orange brown solution was diluted with water until a beige precipitate formed. The precipitate was filtered through a Buchner funnel and washed with water. The crude material was reprecipitated from 1,4-dioxane/ 1N HCl and filtered. Successive fractional recrystallisations in $CHCl_3$ afforded 0.17 g (23%) 205 as an orange amber solid: mp=362-364 °C; R_f 0.80 (A):

R_f 0.88 (B): R_f 0.36 (D): IR (cm^{-1}): 2500-3150 (OH), 3079 (C=CH), 2671 (C-H), 1783 (C=O), 1716 (C=O), 1678 (bs, C=O), 1628 (C=C), 1597 (C=C), 1539 (N=O), 1419 (C=C), 1338 (N-O), 1243 (C-O), 787 (C=CH); MS *m/z* (rel intensity) 361 (100) 317 (52).

3-nitro-N-(*m*-carboxyphenyl)-1,8-naphthalimide (206)

3-nitro-1,8-naphthalic anhydride (0.5 g, 0.0020 mol) and *m*-aminobenzoic acid (0.28 g, 0.0020 mol) were refluxed and the final solution was manipulated as per 205. Crystallization from 1,4-dioxane afforded 0.28 g (39%) of 206 as an yellow amber solid: mp=342-344°C; R_f 0.77 (A): R_f 0.90 (B): R_f 0.56 (D): IR (cm^{-1}): 2800-3125 (OH), 3091(C=CH), 2623 (C-H), 1739 (C=O), 1711 (bs, C=O), 1677 (C=O), 1628 (C=C), 1599 (C=C), 1546 (N=O), 1449 (C=C), 1420 (C=C), 1341 (N-O), 1245 (C-O), 791 (C=CH); MS *m/z* (rel intensity) 361 (100) 317 (30).

3-nitro-N-(*o*-carboxyphenyl)-1,8-naphthalimide (207)

3-nitro-1,8-naphthalic anhydride (0.5 g, 0.0020 mol) and *o*-aminobenzoic acid (0.28 g, 0.0020 mol) were refluxed and the final solution was manipulated as per 205. Crystallization from 1,4-dioxane afforded 0.21 g (29%) of 207 as an orange amber solid: mp=234-237°C; R_f 0.80 (A): R_f 0.80 (B): R_f 0.64 (D): IR (cm^{-1}): 2850-3155 (OH), 3071 (C=CH), 2626 (C-H), 1717 (bs, C=O), 1668 (C=O), 1625 (C=C), 1599 (C=C), 1542 (N=O), 1490 (C=C), 1422 (C=C), 1339 (N-O), 1248 (C-O), 789 (C=CH); MS *m/z* (rel intensity) 361 (100).

3-nitro-N-(*p*-carboxyphenylmethyl)naphthalimide (208)

3-nitro-1,8-naphthalic anhydride (0.5 g, 0.0020 mol) and 4-(aminomethyl)benzoic acid (0.31 g, 0.0020 mol) were refluxed as per 100 overnight. Precipitate that formed during the course of the reaction was filtered and washed with water. A clean product from the mother liquor fraction was not obtained. Crystallization of the product from 1,4-dioxane/H_2O yielded 0.30 g (39%) of 208 as a beige powder: mp=334-336°C; R_f 0.89 (A): R_f 0.71 (C): R_f 0.77 (D): IR (cm^{-1}): 2800-3130 (OH), 3084 (C=CH), 2671 (C-H), 1789 (C=O), 1707 (bs, C=O), 1666

(C=O), 1628 (C=C), 1598 (C=C), 1539 (N=O), 1450 (C=C), 1425 (C=C), 1343 (N-O), 1296 (C-O), 788 (C=CH); MS *m/z* (rel intensity) 375 (100), 331 (48), 172 (57).

4-nitro-N-(*p*-carboxyphenyl)-1,8-naphthalimide (225)

4-nitro-1,8-naphthalic anhydride (0.5 g, 0.0020 mol) and *p*-aminobenzoic acid (0.28 g, 0.0020 mol) were refluxed as per 100 for 48 hours. Precipitate that formed during the course of the reaction was filtered and washed with water. A clean product from the mother liquor fraction was not obtained. Crystallization from 1,4-dioxane/ 1N HCl afforded 0.26 g (35%) of 225 as a beige solid: mp=>320°C; R_f 0.89 (A): R_f 0.82 (B): R_f 0.42 (D); ^{1}H NMR (DMSO-d_6) δ 7.55 (d, *J*=8.3 Hz, 2H), 8.09 (d, *J*=8.3 Hz, 2H), 8.13 (dd, *J*=8.4, 7.7 Hz, 1H), 8.61 (m, 3H), 8.76 (d, *J*=8.4 Hz, 1H); IR (cm^{-1}): 2800-3100 (OH), 3079 (C=CH), 2674 (C-H), 1713 (C=O), 1678 (bs, C=O), 1625 (C=C), 1607 (C=C), 1584 (C=C), 1532 (N=O), 1426 (C=C), 1412 (C=C), 1368 (C-O), 1346 (N-O), 1237 (C-O), 785 (C=CH); MS *m/z* (rel intensity) 362 (22), 361 (100).

4-nitro-N-(*m*-carboxyphenyl)-1,8-naphthalimide (226)

4-nitro-1,8-naphthalic anhydride (0.5 g, 0.0020 mol) and *p*-aminobenzoic acid (0.28 g, 0.0020 mol) were refluxed as per 100 for 48 hours. Precipitate that formed during the course of the reaction was filtered and washed with water. The dark amber filtrate was concentrated to 20 ml *in vacuo* and diluted with 1N HCl until a beige precipitate formed. The precipitate was filtered through a Buchner funnel and washed with water. Crystallization from 1,4-dioxane/ H_2O afforded 0.59 g (81%) of 226 as a beige solid: mp=>320°C; R_f 0.86 (A): R_f 0.82 (B): R_f 0.48 (D): ^{1}H NMR (DMSO-d_6) δ 7.68 (m, 2H), 8.05 (m, 2H), 8.13 (dd, *J*=8.6, 8.4 Hz, 1H), 8.61 (m, 3H), 8.76 (dd, *J*=8.4, 0.8 Hz, 1H); IR (cm^{-1}): 2750-3125 (OH), 3075 (C=CH), 2664 (C-H), 1697 (bs, C=O), 1625 (C=C), 1584 (C=C), 1530 (N=O), 1456 (C=C), 1424 (C=C), 1369 (C-O), 1350 (N-O), 1237 (C-O), 784 (C=CH); MS *m/z* (rel intensity) 362 (22), 361 (100).

Method B:

3-nitro-N-phenyl-1,8-naphthalimide (209)

3-nitro-1,8-naphthalic anhydride (0.5 g, 0.0020 mol) and aniline (0.38 g, 0.0041 mol) were reacted and purified as per 109. Crystallization from $CHCl_3$ afforded 0.38 g (60%) 209 as a beige solid: mp=264-266°C; R_f 0.81 (A): R_f 0.89 (C): R_f 0.77 (D): IR (cm^{-1}): 3085 (C=CH), 2670 (C-H), 1713 (C=O), 1667 (bs, C=O), 1596 (C=C), 1542 (N=O), 1509 (C=C), 1416 (C=C), 1335 (N-O), 1244 (C-O), 707 (C=CH); MS *m/z* (rel intensity) 319 (15), 217 (100) 199 (34) 129 (57).

Example 2 Assessment of NGF/$p75^{NTR}$ binding inhibition

The radio-iodination and receptor binding of NGF (Sutter et al., 1979) was performed with modifications (Ross et al., 1997) as follows: Evaluation of the ability of NCP compounds to inhibit TrkA and $p75^{NTR}$ binding was determined by the binding of ^{125}I-NGF to PC12 cells (rat pheochromocytoma cells expressing TrkA and $p75^{NTR}$; obtained from ATCC) and $PC12^{nnr5}$ (rat pheochromocytoma cells expressing $p75^{NTR}$ only; obtained from Dr. L. Greene, Columbia University, NY). The $p75^{NTR}$ is in a low affinity state and a high affinity state, respectively, in these cell types (Ross et al., 1998). PC12 and $PC12^{nnr5}$ cells were grown in RPMI (Sigma) with 10% heat inactivated donor horse serum and 5% fetal calf serum. Cells were harvested by replacing the medium with calcium, magnesium-free balanced salt solution (Gey's solution) and incubating at 37°C for 15 minutes. Cells were pelleted by centrifugation and suspended in HKR buffer (10 mM Hepes [pH 7.35] containing 125 mM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 1g/L glucose and 1g/L BSA) at a cell concentration of $2x10^6$/mL and kept at 4°C. Triplicate tubes were set up for total binding, non-specific binding and binding in the presence of candidate competitor molecule (i.e., a tube for each data point). Each tube contained ^{125}I-NGF (at 1 nM), 400,000 cells (for a final cell concentration of 10^6/mL) and NGF (50 nM, to define non-specific binding), as required. The tubes were incubated for 2 h at 4°C and specific binding evaluated by measuring specifically bound DPM (Ross et al., 1997). Data were analysed and the results expressed as receptor binding observed in the presence of competitor (e.g. NCP compounds) as a percentage of receptor binding in the absence of a competitor.

Compound (50μM)	PC12 % of Max		nnr5 % of Max	
100	102, 108, 137	Avg = 116	108, 111, 80	Avg = 100
101	89, 94, 139	= 107	89, 91, 64	= 81
102	79, 80, 113	= 91	55, 50, 61	= 55
103	69, 65, 100	= 78	32, 69, 41	= 47
104	51, 50, 66	= 56	30, 65, 17	= 37
105	29, 38, 40	= 36	31, 17, 55	= 34
106	40, 40, 52	= 44	37, 16, 24	= 26
107	111, 86, 103	= 100	58, 113, 83	= 85
107a	101, 116, 110	= 109	67, 115, 78	= 87
108	90, 55, 75	= 73	135, 77, 66	= 93
109	50, 60, 57	= 56	70, 74, 75	= 73
111	90, 96, 101	= 96	67, 70, 111	= 83
120	133, 92, 103	= 109	218, 200, 130	= 183
121	121, 92, 103	= 103	204, 188, 103	= 165
122	106, 88, 98	= 97	232, 152, 104	= 163
123	118, 75, 98	= 97	172, 161, 117	= 150
124	117, 71, 89	= 92	166, 182, 110	= 153
125	83, 87, 99	= 90	47, 54, 47	= 49
126	90, 69, 72	= 77	34, 54, 69	= 52
127	140, 101, 114	= 118	136, 129, 71	= 112
140	100, 126, 108	= 111	89, 108, 100	= 99
141	74, 108, 87	= 90	98, 114, 77	= 96
142	55, 77, 67	= 66	52, 51, 51	= 51
143	65, 97, 72	= 78	76, 79, 71	= 75
144	68, 89, 77	= 78	74, 70, 74	= 73
145	60, 77, 73	Avg = 70	76, 86, 71	Avg = 78

146	52, 52, 71	= 58	48, 43, 42	= 44
165	54, 53, 40	= 49	61, 53, 68	= 61
166	43, 58, 71	= 57	55, 64, 56	= 58
205	16, 19, 15	= 17	0, 11, 15	= 9
206	25, 29, 35	= 30	20, 17, 33	= 23
207	60, 34, 69	= 54	64, 52, 59	= 58
208	56, 45, 47	= 49	103, 87, 58	= 83
209 NS	NT		NT	
225 NS	69, 60, 68	= 66	49, 50, 68	= 56
226 NS	27, 29, 35	= 30	13, 10, 13	= 12

NS: Not Soluble @ 100μM DMSO

NT: Not Tested

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

REFERENCES CITED

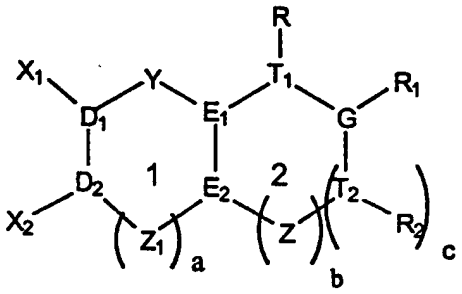
Barbacid, *Oncogene* 8:2033-2042 (1993)
Barde, *Neuron* 2:1525-1534 (1989)
Barker and Shooter, *Neuron* 13:203-215 (1994)
Ben Ari and Represa, *TINS* 13:312-318 (1990)
Berkemeier *et al.*, *Neuron* 7:857-866 (1991)
Bothwell, *Cell* 65:915-918 (1991)
Bothwell and Shooter, *J. Biol. Chem.* 23:8532-8536 (1977)
Bradshaw *et al.*, *Protein Science* 3:1901-1913 (1994)
Burton *et al.*, *J. Neurochem.* 59:1937-1945 (1992)
Burton *et al.*, *Soc. Neurosci. Abs.* 21:1061 (1995)
Carter *et al.*, *Science* 272:542-545 (1996)
Cassacia-Bonnefil *et al.*, *Nature* 383:716-719 (1996)
Chao, *Neuron* 9:583-593 (1992b)
Chao, *J. Neurobiol.* 25:1373-1385 (1994)
Chao and Hempstead, *Trends Neurosci.* 18:321-326 (1995)
Dobrowsky *et al.*, *Science* 265:1596-1599 (1994)
Drinkwater *et al.*, *J. Biol. Chem.* 268:23202-23207 (1993)
Escandon *et al.*, *Neurosci. Res.* 34:601-613 (1993)
Gotz *et al.*, *Nature* 372:266-269 (1994)
Gregory *et al.*, *Protein Engineering* 6:29-35 (1993)
Hallböök *et al.*, *Neuron* 6:845-858 (1991)
Hefti, *J. Neurosci.* 6:2155-2162 (1986)
Hefti and Weiner, *Annals of Neurology* 20:275-281 (1986)
Heldin *et al.*, *J. Biol. Chem.* 264:8905-8912 (1989)
Hempstead *et al.*, *Nature* 350:678-683 (1991)
Herrmann *et al.*, *Mol. Biol.* 4:1205-1216 (1993)
Hohn *et al.*, *Nature* 344:339-341 (190)
Ibáñez *et al.*, *Cell* 69:329-341 (1992)
Ibáñez *et al.*, *EMBO J.* 12:2281-2293 (1993)
Ibáñez, *Trends Biotech.* 13:217-227 (1995)
Jing *et al.*, *Neuron* 9:1067-1079 (1992)
Kahle *et al.*, *J. Biol. Chem.* 267:22707-22710 (1992)
Kaplan *et al.*, *Science* 252:554-558 (1991)
Klein *et al.*, *Cell* 65:189-197 (1991)
Klein *et al.*, *Neuron* 8:947-956 (1992)
Lamballe *et al.*, *Cell* 66:967-970 (1991)
Landreth and Shooter, *Proc. Natl. Acad. Sci. U.S.A.* 77:4751-4755 (1980)
Leibrock *et al.*, *Nature* 341:149-152 (1989)
Leven and Mendel, *TINS* 16:353-359 (1993)

Levi-Montalcini, *EMBO J.* 6:1145-1154 (1987)
Luo and Neet, *J. Biol. Chem.* 267:12275-12283 (1992)
Mahadeo *et al.*, *J. Biol. Chem.* 269:6884-6891 (1994)
Maisonpierre *et al.*, *Science* 247:1446-1451 (1990)
Maness *et al.*, *Neurosci. Biobehav. Rev.* 18:143-159 (1994)
Marchetti *et al.*, *Cancer Res.* 56:2856-2863 (1996)
Matsumoto *et al.*, *Cancer Res.* 55:1798-1806 (1995)
McDonald *et al.*, *Nature* 354:411-414 (1991)
McKee *et al.*, *Ann. Neurol.* 30:156 (1991)
McMahon *et al.*, *Nature Med.* 1:774-780 (1995)
Meakin and Shooter, *Trends Neurosci.* 15:323-331 (1992)
Moore and Shooter, *Neurobiology* 5:369-381 (1975)
Radziejewski *et al.*, *Biochemistry* 31:4431-4436 (1992)
Rashid *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 92:9495-9499 (1995)
Rodrigues-Tébar *et al.*, *Neuron* 4:487-492 (1990)
Rodrigues-Tébar *et al.*, *EMBO J.* 11:917-922 (1992)
Rosenthal *et al.*, *Neuron* 4:767-773 (1990)
Ross *et al.*, *J. Cell Biol.* 132:945-953 (1996)
Ross *et al.*, *Nature Med.* 3:872-878 (1997)
Ross *et al. Eur. J. Neurosci.* 10 890-898 (1998)
Rydén and Ibáñez, *J. Biol. Chem.* 271:5623-5627 (1996)
Schechter and Bothwell, *Cell* 24:867-874 (1981)
Shamovsky et *al.*, *Can. J. Chem.* 76:1389-1401 (1998)
Shamovsky et al., *J. Am Chem Soc* 118:9743-9749 (1999)
Shih *et al.*, *J. Biol. Chem.* 269:27679-27686 (1994)
Soppet *et al.*, *Cell* 65:895-903 (1991)
Squinto *et al.*, *Cell* 65:885-893 (1991)
Suter *et al.*, *J. Neurosci.* 12:306-318 (1992)
Sutter *et al.*, *J. Biol. Chem.* 254:5972-5982 (1979)
Taylor *et al.*, *Soc. Neurosci. Abs.* 17:712 (1991)
Treanor *et al.*, *J. Biol. Chem.* 270:23104-23110 (1995)
Vale and Shooter, *Methods Enzymol.* 109:21-39 (1985)
Van der Zee *et al.*, *Science* 274:1729-1732 (1996)
Washiyama *et al.*, *Amer. J. Path.* 148:929-940 (1996)
Wolf *et al.*, *J. Biol. Chem.* 270:2133-2138 (1995)
Woolf and Doubell, *Current Opinions in Neurobiol.* 4:525-534 (1994)

CLAIMS

What is claimed is:

1. A method of inhibiting the binding of nerve growth factor to the $p75^{NTR}$ receptor, comprising contacting the cells expressing the $p75^{NTR}$ receptor with an effective inhibiting amount of a compound of Formula 1,



(1)

wherein

D_1, D_2, E_1, E_2 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom;

one of X_1 and X_2 is a hydrogen atom or absent, while the other is an electronegative atom or an electronegative functional group;

R and R_2 are each, independently, an electronegative atom or an electronegative functional group;

Y is N, O, S, C-L or N-L, where L is H, alkyl or an electronegative atom or functional group;

Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl, N-cycloalkyl or N-P, where P is a carbohydrate moiety;

T_1 and T_2 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom;

a, b and c are each 0 or 1, provided that at least one of b and c is 1; and

R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamino or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups.

2. The method of Claim 1 wherein

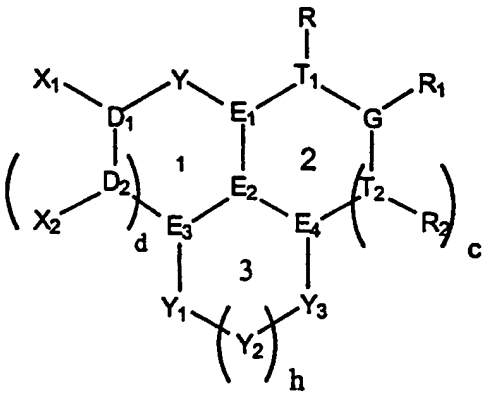
X is alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; PO_3H_2; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl group or a fluorine, chlorine, bromine or iodine atom;

R and R_2 are each, independently, O, S, CH_2 or NR_3, where R_3 is H, alkyl or aryl; and

R_1 is a monocyclic or polycyclic aryl or heteroaryl, alkyl, cycloalkyl, arylalkyl, monosaccharide or oligosaccharide group, said group being substituted with at least one substituent selected from the group consisting of alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; $-PO_3H_2$; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, carboxyalkyl, nitroalkyl, N,N-dialkylaminosulfonyl, aminocarbonyl, methoxycarbonyl, methoxycarbonylalkyl, cyanocarbonylalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, acetamido, fluorine, chlorine, bromine and iodine ;or

R_1 is selected from the group consisting of $-(CH_2)_aPO_3H_2$; $-(CH_2)_aNO_2$; $-(CH_2)_aOH$; $-(CH_2)_aSO_3H$; $-(CH_2)_aSO_2H$; $O(CH_2)_aPO_3H_2$; $-O(CH_2)_aCOOH$; $-O(CH_2)_aNO_2$; $-O(CH_2)_aSO_2H$; $-O(CH_2)_aSO_3H$; $-O(CH_2)_aOH$; $-NH(CH_2)_aCOOH$; $-NH(CH_2)_aNO_2$; $-NH(CH_2)_aSO_2H$; $-NH(CH_2)_aPO_3H_2$ and $NH(CH_2)_aSO_3H$; wherein a is1 to about 4.

3. A method of inhibiting the binding of nerve growth factor to the $p75^{NTR}$ receptor, comprising contacting the cells expressing the $p75^{NTR}$ receptor with an effective inhibiting amount of a compound of Formula 3,



(3)

wherein

D_1, D_2, E_1, E_2 E_3, E_4 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom;

one of X_1 and X_2 is a hydrogen atom, while the other is an electronegative atom or an electronegative functional group;

R and R_2 are each, independently, an electronegative atom or an electronegative functional group;

Y, Y_1, Y_2, and Y_3 are each, independently, N, O, S, C-L or N-L, where L is H, alkyl or an electronegative atom or functional group;

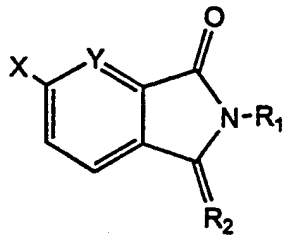
T_1 and T_2 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom;

d, h and c are each 0 or 1; and

R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide which is substituted with at least one acid functional group.

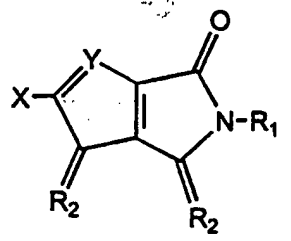
4. The method of Claim 3 wherein R_1 is a mono- or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide group which is substituted with at least one acid functional group selected from the group consisting of alkyl-CO_2H; alkyl-SO_3H; alkyl-SO_2H; alkyl-PO_3H_2; alkyl-OSO_3H.

5. The method of Claim 1 wherein the compound is of the general formula



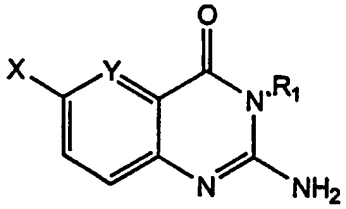
wherein X, Y and R_1 have the meanings given for these variables in Claim 1 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

6. The method of Claim 1 wherein the compound is of the general formula



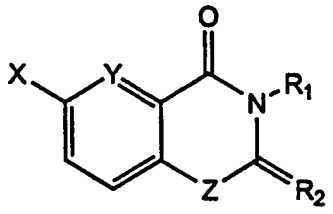
wherein X, Y and R_1 have the meanings given for these variables in Claim 1 and each R_2 is independently O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

7. The method of Claim 1 wherein the compound is of the general formula



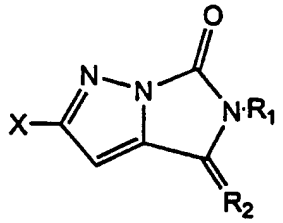
wherein X, Y and R_1 have the meanings given for these variables in Claim 1.

8. The method of Claim 1 wherein the compound is of the general formula



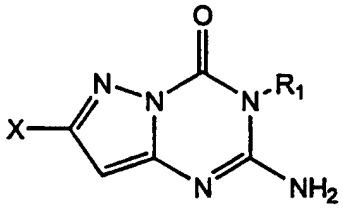
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 1 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

9. The method of Claim 1 wherein the compound is of the general formula



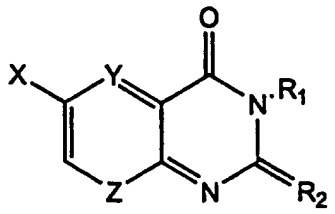
wherein X and R_1 have the meanings given for these variables in Claim 1 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

10. The method of Claim 1 wherein the compound is of the general formula



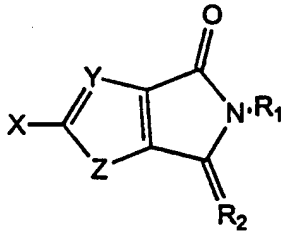
wherein X and R_1 have the meanings given for these variables in Claim 1.

11. The method of Claim 1 wherein the compound is of the general formula



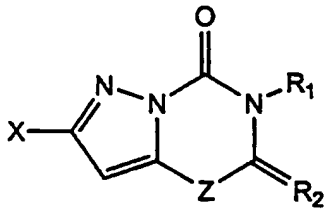
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 1 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

12. The method of Claim 1 wherein the compound is of the general formula



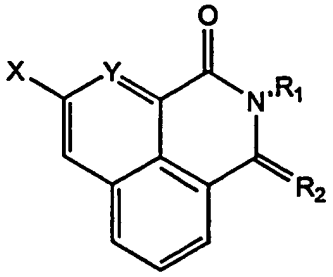
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 1 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

13. The method of Claim 1 wherein the compound is of the general formula



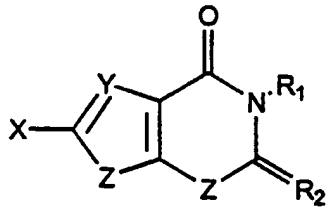
wherein X, Z and R_1 have the meanings given for these variables in Claim 1 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

14. The method of Claim 3 wherein the compound is of the general formula



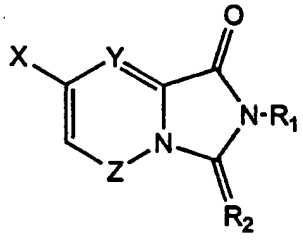
wherein X, Y and R_1 have the meanings given for these variables in Claim 1 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

15. The method of Claim 1 wherein the compound is of the general formula



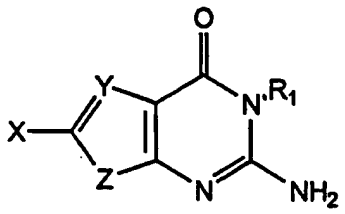
wherein X, Y, R_1 have the meanings given for these variables in Claim 1, each Z, independently, has one of the meanings given for Z in Claim 1,and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

16. The method of Claim 1 wherein the compound is of the general formula



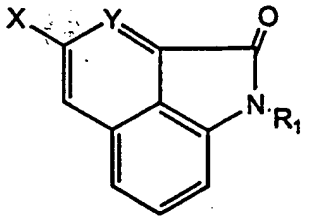
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 1 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

17. The method of Claim 1 wherein the compound is of the general formula



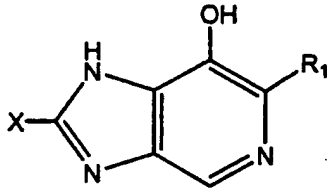
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 1.

18. The method of Claim 3 wherein the compound is of the general formula



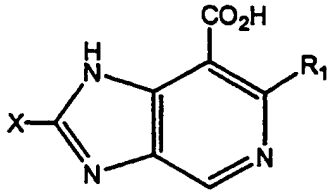
wherein X, Y and R_1 have the meanings given for these variables in Claim 3.

19. The method of Claim 1 wherein the compound is of the formula



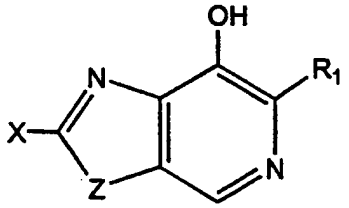
wherein X and R_1 have the meanings given for these variables in Claim 1.

20. The method of Claim 1 wherein the compound is of the formula



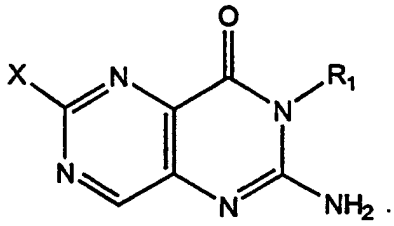
wherein X and R_1 have the meanings given for these variables in Claim 1.

21. The method of Claim 1 wherein the compound is of the formula



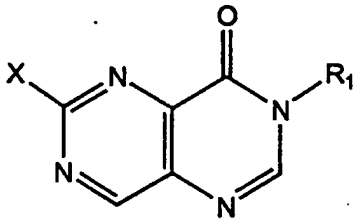
wherein X, Z and R_1 have the meanings given for these variables in Claim 1.

22. The method of Claim 1 wherein the compound is of the formula



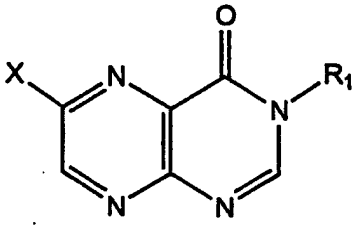
wherein X and R_1 have the meanings given for these variables in Claim 1.

23. The method of Claim 1 wherein the compound is of the formula



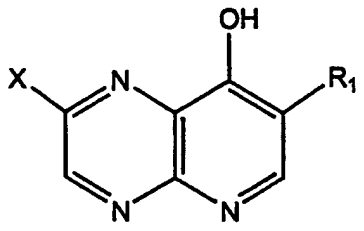
wherein X and R_1 have the meanings given for these variables in Claim 1.

24. The method of Claim 1 wherein the compound is of the formula



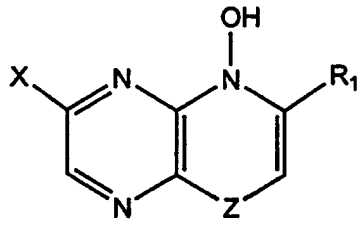
wherein X and R_1 have the meanings given for these variables in Claim 1.

25. The method of Claim 1 wherein the compound is of the formula



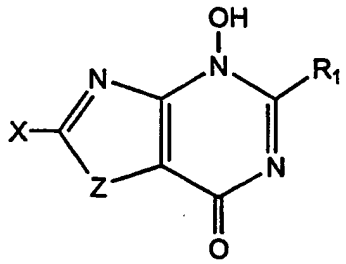
wherein X and R_1 have the meanings given for these variables in Claim 1.

26. The method of Claim 1 wherein the compound is of the formula



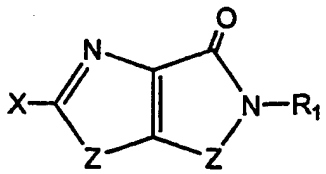
wherein X, Z and R_1 have the meanings given for these variables in Claim 1.

27. The method of Claim 1 wherein the compound is of the formula



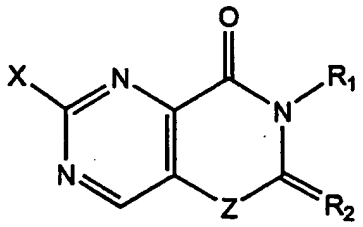
wherein X, Z and R_1 have the meanings given for these variables in Claim 1.

28. The method of Claim 1 wherein the compound is of the formula



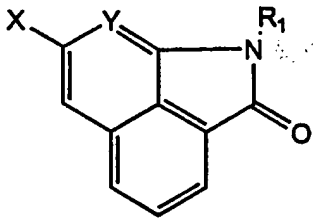
wherein X and R_1 have the meanings given for these variables in Claim 1 and each Z, independently, has one of the meanings given for Z in Claim 1.

29. The method of Claim 3 wherein the compound is of the formula



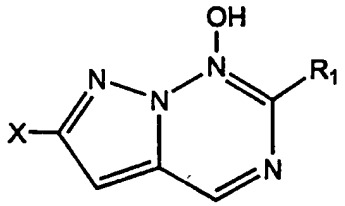
wherein X, Z and R_1 have the meanings given for these variables in Claim 1, and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

30. The method of Claim 3 wherein the compound is of the formula



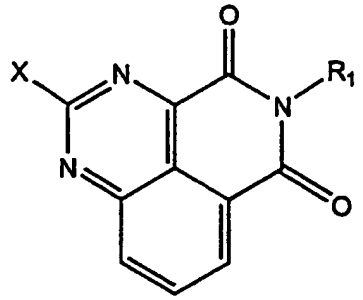
wherein X, Y and R_1 have the meanings given for these variables in Claim 3.

31. The method of Claim 1 wherein the compound is of the formula



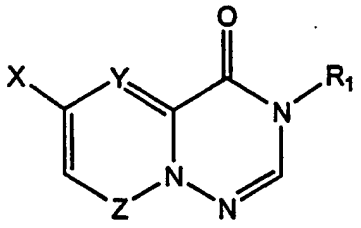
wherein X and R_1 have the meanings given for these variables in Claim 1.

32. The method of Claim 3 wherein the compound is of the formula



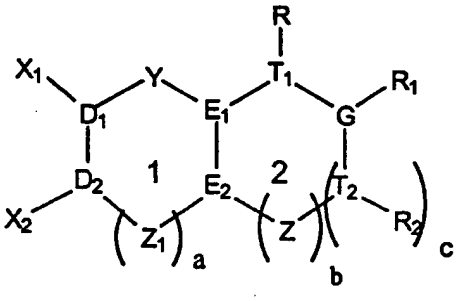
wherein X and R_1 have the meanings given for these variables in Claim 3.

33. The method of Claim 1 wherein the compound is of the formula



wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 1.

34. A method of treating a condition characterized by nerve growth factor-mediated cell apoptosis in a patient; said method comprising the step of administering to the patient a therapeutically effective amount of a compound of Formula 1,



(1)

wherein

D_1, D_2, E_1, E_2 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom;

one of X_1 and X_2 is a hydrogen atom or absent, while the other is an electronegative atom or an electronegative functional group;

R and R_2 are each, independently, an electronegative atom or an electronegative functional group;

Y is N, O, S, C-L or N-L, where L is H, alkyl or an electronegative atom or functional group;

Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl, N-cycloalkyl or N-P, where P is a carbohydrate moiety;

T_1 and T_2 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom;

a, b and c are each 0 or 1, provided that at least one of b and c is 1; and

R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamino or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups.

35. The method of Claim 34 wherein

X is alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; PO_3H_2; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl group or a fluorine, chlorine, bromine or iodine atom;

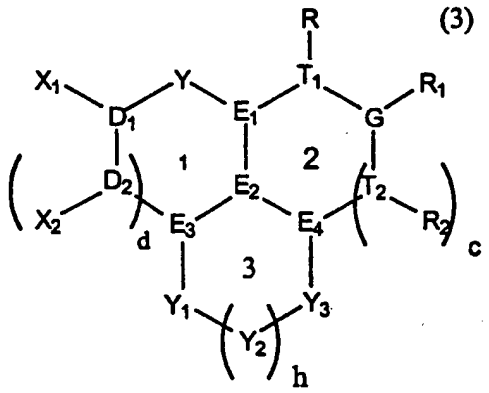
R and R_2 are each, independently, O, S, CH_2 or NR_3, where R_3 is H, alkyl or aryl; and

R_1 is a monocyclic or polycyclic aryl or heteroaryl group substituted with at least one substituent selected from the group consisting of alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; $-PO_3H_2$; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, carboxyalkyl, nitroalkyl, N,N-dialkylaminosulfonyl, aminocarbonyl, methoxycarbonyl, methoxycarbonylalkyl, cyanocarbonylalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, acetamido, fluorine, chlorine, bromine and iodine ;or

R_1 is selected from the group consisting of $-(CH_2)_aPO_3H_2$; $-(CH_2)_aNO_2$; $-(CH_2)_aOH$; $-(CH_2)_aSO_3H$; $-(CH_2)_aSO_2H$; $O(CH_2)_aPO_3H_2$;

$-O(CH_2)_aCOOH$; $-O(CH_2)_aNO_2$; $-O(CH_2)_aSO_2H$; $-O(CH_2)_aSO_3H$; $-O(CH_2)_aOH$; $-NH(CH_2)_aCOOH$; $-NH(CH_2)_aNO_2$; $-NH(CH_2)_aSO_2H$; $-NH(CH_2)_aPO_3H_2$ and $NH(CH_2)_aSO_3H$; wherein a is 0 to about 4.

36. A method of treating a condition characterized by nerve growth factor-mediated cell apoptosis in a patient; said method comprising the step of administering to the patient a therapeutically effective amount of a compound of Formula 3,



wherein

D_1, D_2, E_1, E_2 E_3, E_4 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom;

one of X_1 and X_2 is a hydrogen atom, while the other is an electronegative atom or an electronegative functional group;

R and R_2 are each, independently, an electronegative atom or an electronegative functional group;

Y, Y_1, Y_2, and Y_3 are each, independently, N, O, S, C-L or N-L, where L is H, alkyl or an electronegative atom or functional group;

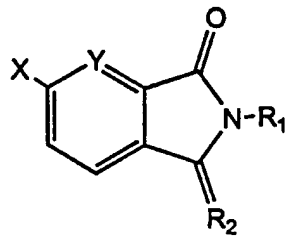
T_1 and T_2 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom;

d, h and c are each 0 or 1is 1; and

R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or

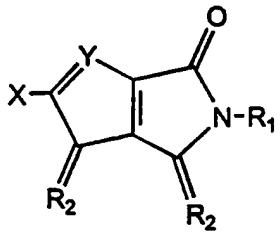
oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamino or alkoxy group which is substituted with at least one substituent selected from the group consisting of acid functional groups.

37. The method of Claim 34 wherein the compound is of the general formula



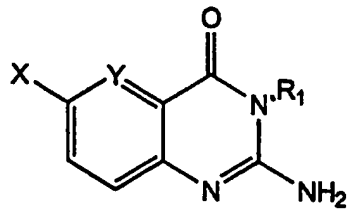
wherein X, Y and R_1 have the meanings given for these variables in Claim 34 and R_2 is O, S or CH_2.

38. The method of Claim 34 wherein the compound is of the general formula



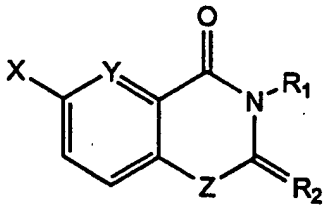
wherein X, Y and R_1 have the meanings given for these variables in Claim 34 and each R_2 is independently O, S, CH_2 or N-R_4, wherein R_4 is H, OH, alkyl or aryl.

39. The method of Claim 34 wherein the compound is of the general formula



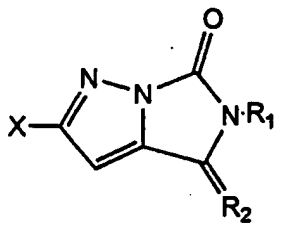
wherein X, Y and R_1 have the meanings given for these variables in Claim 34.

40. The method of Claim 34 wherein the compound is of the general formula



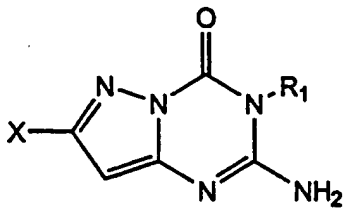
wherein X, Y and R_1 have the meanings given for these variables in Claim 34 and R_2 is O, S or CH_2.

41. The method of Claim 34 wherein the compound is of the general formula



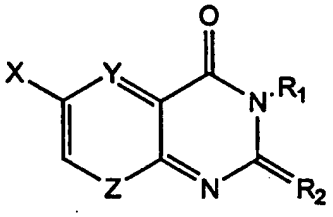
wherein X and R_1 have the meanings given for these variables in Claim 34 and R_2 is O, S or CH_2.

42. The method of Claim 34 wherein the compound is of the general formula



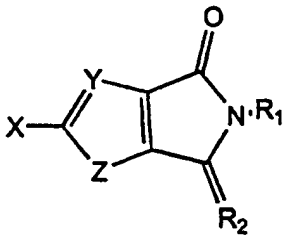
wherein X and R_1 have the meanings given for these variables in Claim 34.

43. The method of Claim 34 wherein the compound is of the general formula



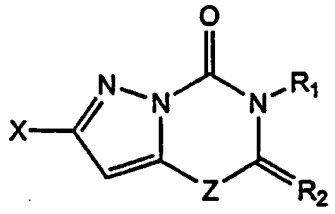
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 34 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl or aryl.

44. The method of Claim 34 wherein the compound is of the general formula



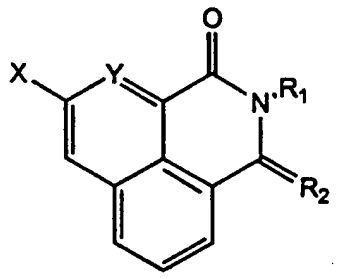
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 34 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

45. The method of Claim 34 wherein the compound is of the general formula



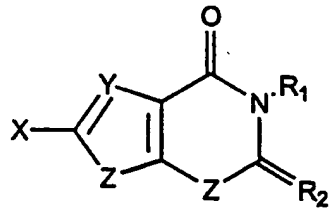
wherein X, Z and R_1 have the meanings given for these variables in Claim 34 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

46. The method of Claim 36 wherein the compound is of the general formula



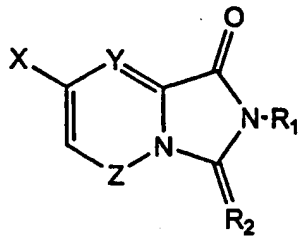
wherein X, Y and R_1 have the meanings given for these variables in Claim 36 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

47. The method of Claim 34 wherein the compound is of the general formula



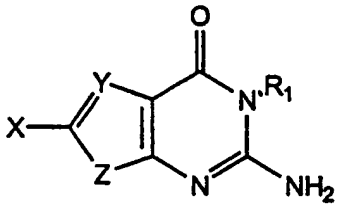
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 34 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

48. The method of Claim 34 wherein the compound is of the general formula



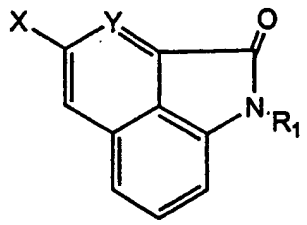
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 34 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

49. The method of Claim 34 wherein the compound is of the general formula



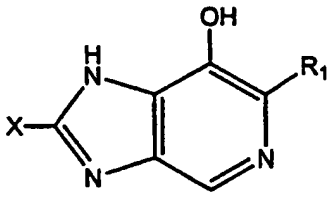
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 34.

50. The method of Claim 36 wherein the compound is of the general formula



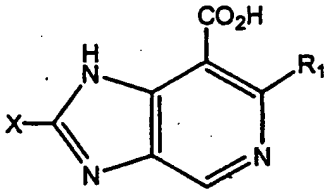
wherein X, Y and R_1 have the meanings given for these variables in Claim 36.

51. The method of Claim 34 wherein the compound is the formula



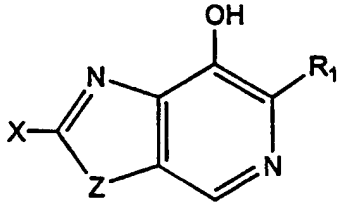
wherein X and R_1 have the meanings given for these variables in Claim 34.

52. The method of Claim 34 wherein the compound is of the formula



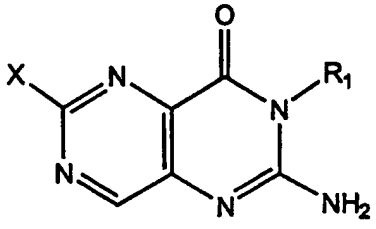
wherein X and R_1 have the meanings given for these variables in Claim 34.

53. The method of Claim 34 wherein the compound is of the formula



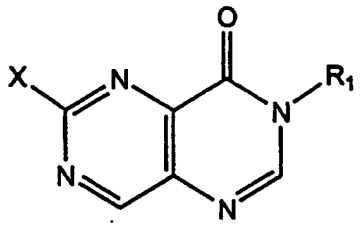
wherein X and R_1 have the meanings given for these variables in Claim 34.

54. The method of Claim 34 wherein the compound is of the formula



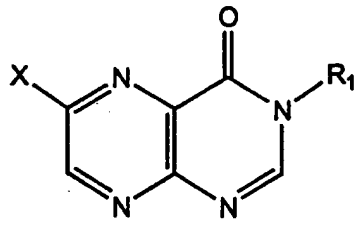
wherein X and R_1 have the meanings given for these variables in Claim 34.

55. The method of Claim 34 wherein the compound is of the formula



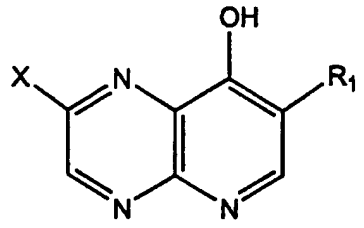
wherein X and R_1 have the meanings given for these variables in Claim 34.

56. The method of Claim 34 wherein the compound is of the formula



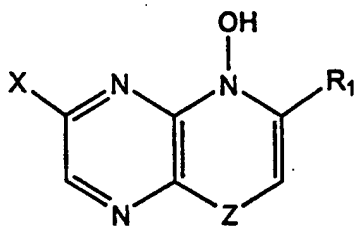
wherein X and R_1 have the meanings given for these variables in Claim 34.

57. The method of Claim 34 wherein the compound is of the formula



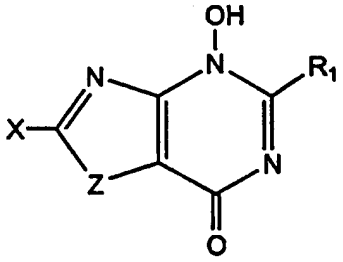
wherein X and R_1 have the meanings given for these variables in Claim 34.

58. The method of Claim 34 wherein the compound is of the formula



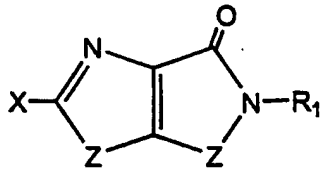
wherein X, Z and R_1 have the meanings given for these variables in Claim 34.

59. The method of Claim 34 wherein the compound is of the formula



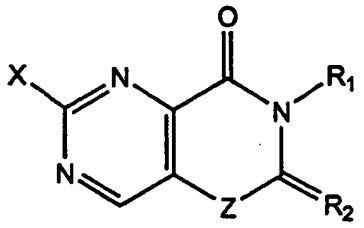
wherein X, Z and R_1 have the meanings given for these variables in Claim 34.

60. The method of Claim 34 wherein the compound is of the formula



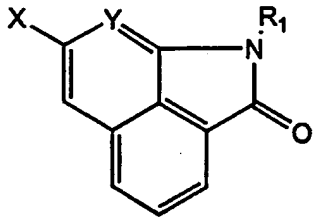
wherein X, Z and R_1 have the meanings given for these variables in Claim 34.

61. The method of Claim 34 wherein the compound is of the formula



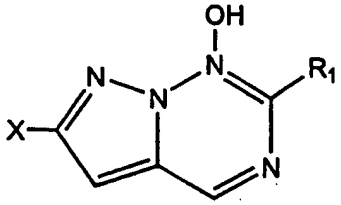
wherein X, Z and R_1 have the meanings given for these variables in Claim 34.

62. The method of Claim 36 wherein the compound is of the formula



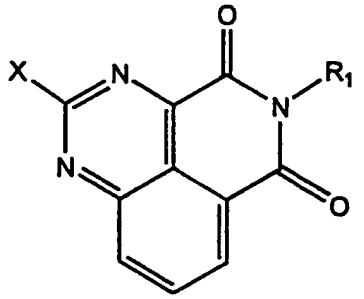
wherein X, Y and R_1 have the meanings given for these variables in Claim 36.

63. The method of Claim 34 wherein the compound is of the formula



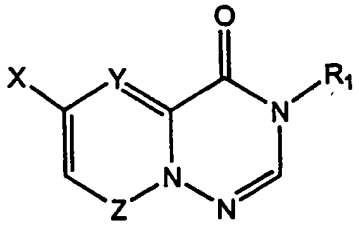
wherein X and R_1 have the meanings given for these variables in Claim 34.

64. The method of Claim 36 wherein the compound is of the formula



wherein X and R_1 have the meanings given for these variables in Claim 36.

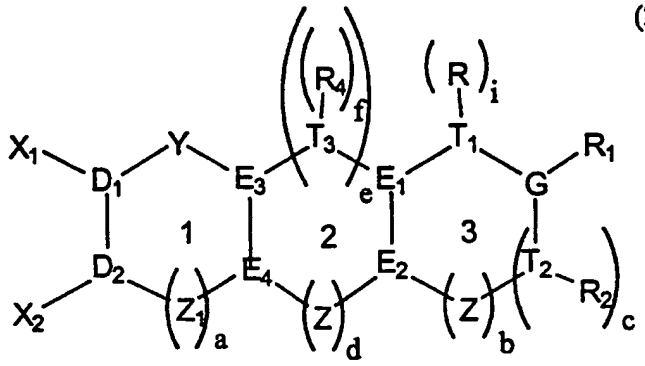
65. The method of Claim 34 wherein the compound is of the formula



wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 34.

66. A method for treating a neurotrophin-mediated condition in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula 2,

(2)



wherein

D_1, D_2, E_1, E_2 , E_3, E_4 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom;

one of X_1 and X_2 is a hydrogen atom or absent, while the other is an electronegative atom or an electronegative functional group;

R, R_2 and R_4 are each, independently, an electronegative atom or an electronegative functional group;

a, b, c, d, e and f are 0 or 1, provided that at least one of b and c is 1 and at least one of b and e is 1;

Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl, N-cycloalkyl and N-P, where P is a carbohydrate moiety;

T_1, T_2 and T_3 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom; or when f is 0, T_3 can further have the meanings given for Z and Z_1;

a, b, c, d, e, f and i are each 0 or 1, provided that at least one of b and c is 1, at least one of d and e is 1 and at least one of f and i is 1;

R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamine or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups.

67. The method of Claim 66 wherein

X is alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; PO_3H_2; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl group or a fluorine, chlorine, bromine or iodine atom;

R_1 and R_2 are each, independently, O, S, CH_2 or NR_3, where R_3 is H, OH alkyl or aryl; and

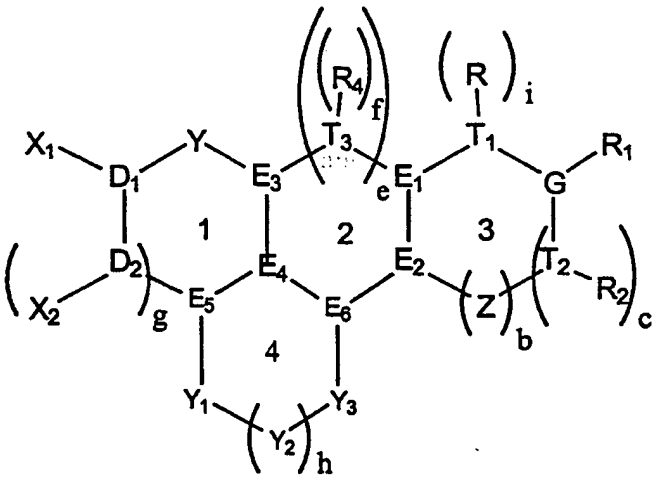
R_1 is a monocyclic or polycyclic aryl or heteroaryl group substituted with at least one substituent selected from the group consisting of alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; $-PO_3H_2$; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, carboxyalkyl, nitroalkyl, N,N-dialkylaminosulfonyl, aminocarbonyl, methoxycarbonyl, methoxycarbonylalkyl, cyanocarbonylalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, acetamido, fluorine, chlorine, bromine and iodine ;or

R_1 is selected from the group consisting of $-(CH_2)_aPO_3H_2$; $-(CH_2)_aNO_2$; $-(CH_2)_aOH$; $-(CH_2)_aSO_3H$; $-(CH_2)_aSO_2H$; $O(CH_2)_aPO_3H_2$;

$-O(CH_2)_aCOOH$; $-O(CH_2)_aNO_2$; $-O(CH_2)_aSO_2H$; $-O(CH_2)_aSO_3H$; $-O(CH_2)_aOH$; $-NH(CH_2)_aCOOH$; $-NH(CH_2)_aNO_2$; $-NH(CH_2)_aSO_2H$; $-NH(CH_2)_aPO_3H_2$ and $NH(CH_2)_aSO_3H$; wherein a is 1 to about 4.

68. A method for treating a neurotrophin-mediated condition in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula 5,

(5),



wherein

D_1, D_2, E_1, E_2 , E_3, E_4, E_5, E_6 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom;

one of X_1 and X_2 is a hydrogen atom, while the other is an electronegative atom or an electronegative functional group;

R, R_2 and R_4 are each, independently, an electronegative atom or an electronegative functional group;

a, b, c, d, e , f, g, h and i are each 0 or 1, provided that at least one of b and c is 1, and at least one of f and i is 1;

Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl, N-cycloalkyl and N-P, where P is a carbohydrate moiety;

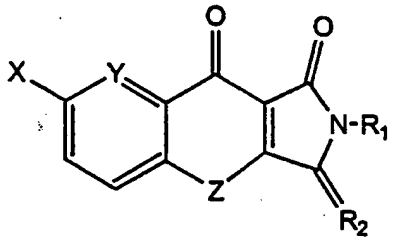
T_1, T_2 and T_3 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom; or when f is 0, T_3 can further have the meanings given for Z and Z_1;

a, b, c, d and e are each 0 or 1, provided that at least one of b and c is 1 and at

least one of d and e is 1;

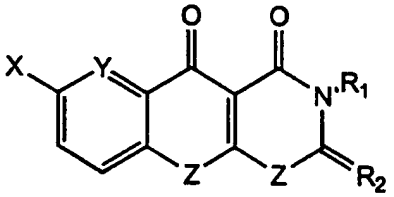
R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamine or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups.

69. The method of Claim 66 wherein the compound is of the general formula



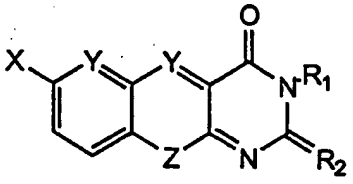
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl or aryl.

70. The method of Claim 66 wherein the compound is of the general formula



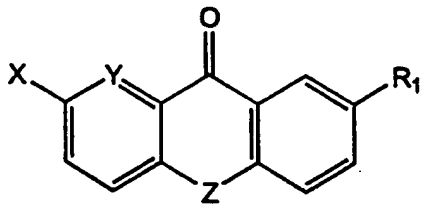
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

71. The method of Claim 66 wherein the compound is of the general formula



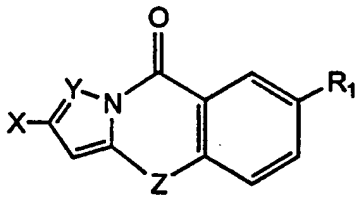
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

72. The method of Claim 66 wherein the compound is of the general formula



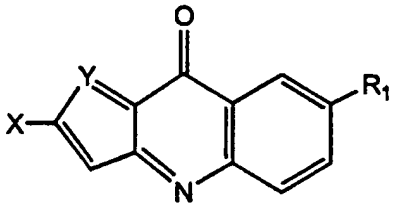
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

73. The method of Claim 66 wherein the compound is of the general formula



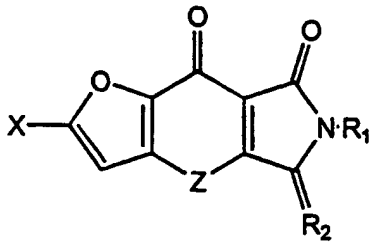
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

74. The method of Claim 68 wherein the compound is of the general formula



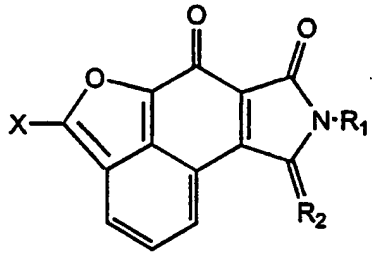
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

75. The method of Claim 66 wherein the compound is of the general formula



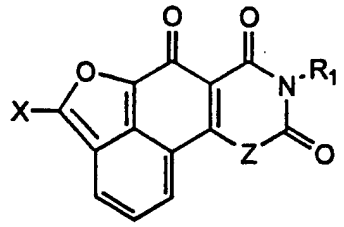
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

76. The method of Claim 68 wherein the compound is of the general formula



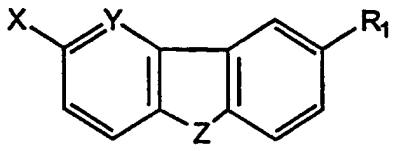
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 68 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

77. The method of Claim 68 wherein the compound is of the general formula



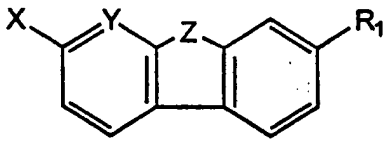
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 68 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

78. The method of Claim 66 wherein the compound is of the general formula



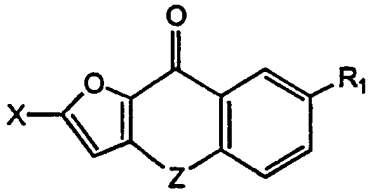
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

79. The method of Claim 66 wherein the compound is of the general formula



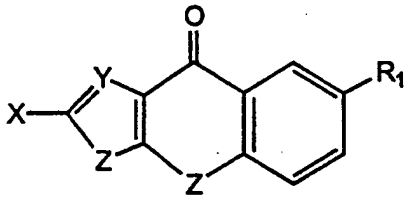
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

80. The method of Claim 66 wherein the compound is of the general formula



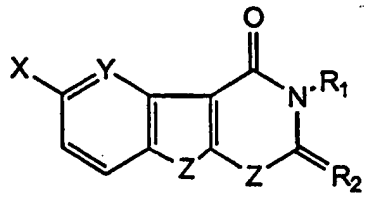
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

81. The method of Claim 66 wherein the compound is of the general formula



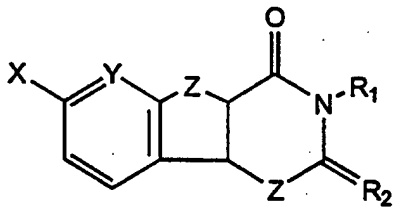
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

82. The method of Claim 66 wherein the compound is of the general formula



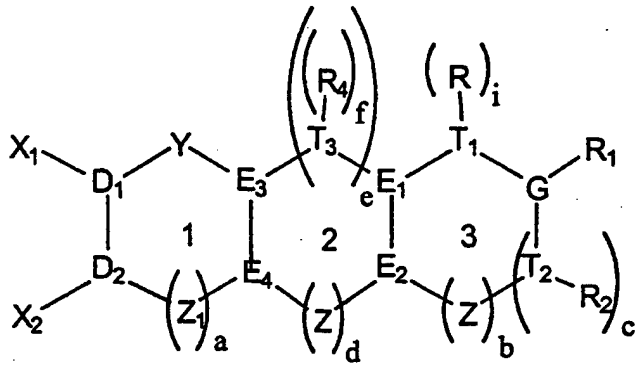
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

83. The method of Claim 66 wherein the compound is of the general formula



wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 66 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

84. A method of treating a condition characterized by nerve growth factor-mediated cell apoptosis in a patient; said method comprising the step of administering to the patient a therapeutically effective amount of a compound of Formula 2,



(2),

wherein

D_1, D_2, E_1, E_2 , E_3, E_4 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom;

one of X_1 and X_2 is a hydrogen atom or absent, while the other is an electronegative atom or an electronegative functional group;

R, R_2 and R_4 are each, independently, an electronegative atom or an electronegative functional group;

a, b, c, d, e ,f and i are 0 or 1, provided that at least one of b and c is 1, at least one of b and e is 1 and at least one of f and i is 1;

Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl, N-cycloalkyl and N-P, where P is a carbohydrate moiety;

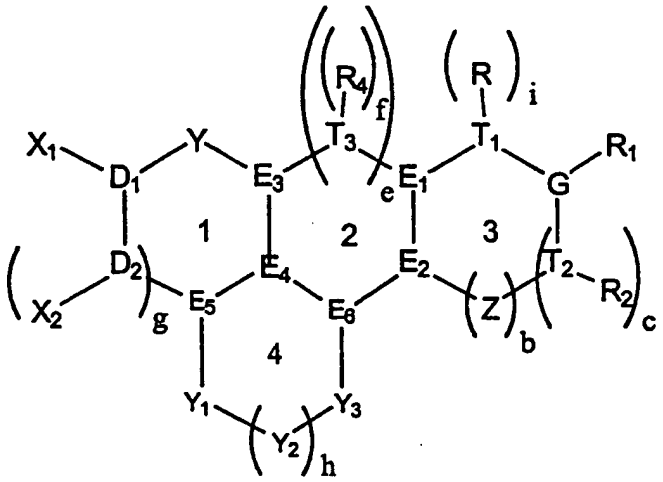
T_1, T_2 and T_3 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom; or when f is 0, T_3 can further have the meanings given for Z and Z_1;

a, b, c, d and e are each 0 or 1, provided that at least one of b and c is 1 and at least one of d and e is 1;

R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamine or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups.

85. A method of treating a condition characterized by nerve growth factor-mediated cell apoptosis in a patient; said method comprising the step of administering to the patient a therapeutically effective amount of a compound of Formula 5,

(5),



wherein

D_1, D_2, E_1, E_2 , E_3, E_4, E_5, E_6 and G are each, independently, an sp^2-hybridized carbon or nitrogen atom;

one of X_1 and X_2 is a hydrogen atom, while the other is an electronegative atom or an electronegative functional group;

R, R_2 and R_4 are each, independently, an electronegative atom or an electronegative functional group;

b, c, f, g, h and i are 0 or 1, provided that at least one of b and c is 1 and one of f and i is 1;

Z and Z_1 are each, independently, O, S, CH, C(O), N, NH, N-alkyl, N-cycloalkyl and N-P, where P is a carbohydrate moiety;

T_1, T_2 and T_3 are each, independently, an sp^2- or sp^3-hybridized carbon or nitrogen atom; or when f is 0, T_3 can further have the meanings given for Z and Z_1;

R_1 is a monocyclic or polycyclic aryl or heteroaryl, monosaccharide or oligosaccharide, alkyl, cycloalkyl, arylalkyl, alkylamine or alkoxy group which is substituted with at least one substituent selected from the group consisting of electronegative atoms and electronegative functional groups.

86. The method of Claim 84 wherein

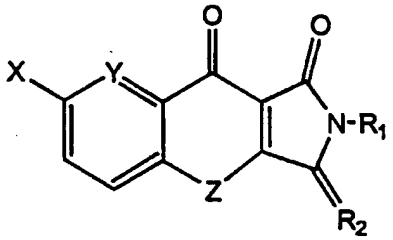
X is alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; aminocarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; PO_3H_2; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, -OC(O)(OH); halomethyl, dihalomethyl or trihalomethyl group or a fluorine, chlorine, bromine or iodine atom;

R and R2 are each, independently, O, S, CH_2 or NR_3, where R_3 is H, alkyl or aryl; and

R_1 is a monocyclic or polycyclic aryl or heteroaryl group substituted with at least one substituent selected from the group consisting of alkylcarbonyl; alkylthiocarbonyl; alkoxycarbonyl; -OH; -CN; $-CO_2H$; $-SO_3H$; $-SO_2H$; $-PO_3H_2$; $-NO_2$; $-ONO_2$, -CNO, -SH, -CNS, $-OSO_3H$, carboxyalkyl, nitroalkyl, N,N-dialkylaminosulfonyl, aminocarbonyl, methoxycarbonyl, methoxycarbonylalkyl, cyanocarbonylalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, acetamido, fluorine, chlorine, bromine and iodine ;or

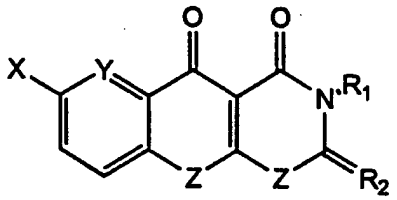
R_1 is selected from the group consisting of $-(CH_2)_aPO_3H_2$; $-(CH_2)_aNO_2$; $-(CH_2)_aOH$; $-(CH_2)_aSO_3H$; $-(CH_2)_aSO_2H$; $O(CH_2)_aPO_3H_2$; $-O(CH_2)_aCOOH$; $-O(CH_2)_aNO_2$; $-O(CH_2)_aSO_2H$; $-O(CH_2)_aSO_3H$; $-O(CH_2)_aOH$; $-NH(CH_2)_aCOOH$; $-NH(CH_2)_aNO_2$; $-NH(CH_2)_aSO_2H$; $-NH(CH_2)_aPO_3H_2$ and $NH(CH_2)_aSO_3H$; wherein a is1 to about 4.

87. The method of Claim 84 wherein the compound is of the general formula



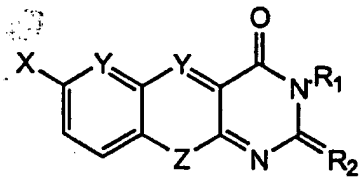
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

88. The method of Claim 84 wherein the compound is of the general formula



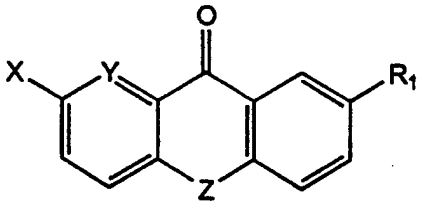
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

89. The method of Claim 84 wherein the compound is of the general formula



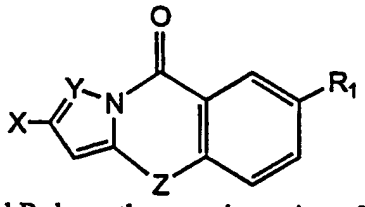
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

90. The method of Claim 84 wherein the compound is of the general formula



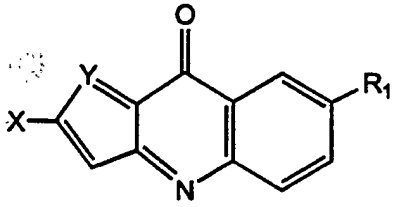
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

91. The method of Claim 84 wherein the compound is of the general formula



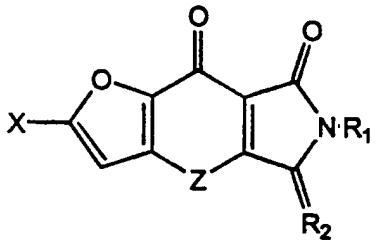
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

92. The method of Claim 84 wherein the compound is of the general formula



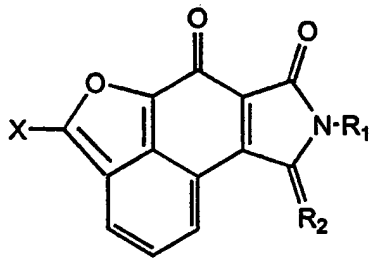
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

93. The method of Claim 84 wherein the compound is of the general formula



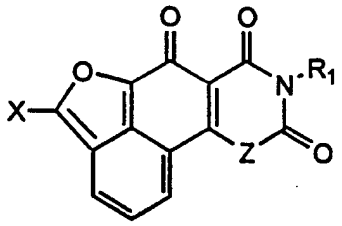
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

94. The method of Claim 85 wherein the compound is of the general formula



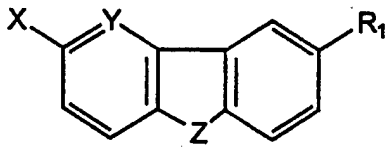
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 85 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

95. The method of Claim 85 wherein the compound is of the general formula



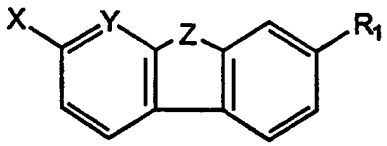
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 95 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

96. The method of Claim 84 wherein the compound is of the general formula



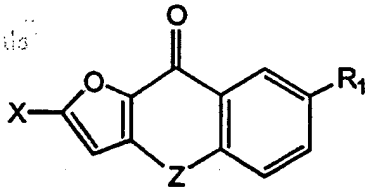
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

97. The method of Claim 84 wherein the compound is of the general formula



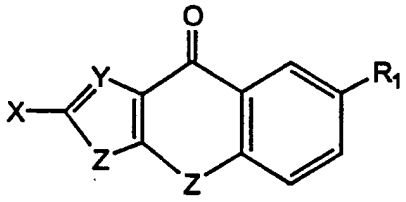
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

98. The method of Claim 84 wherein the compound is of the general formula



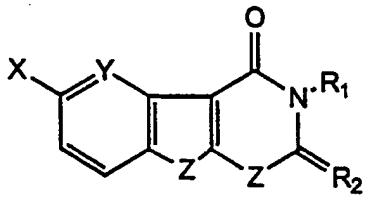
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

99. The method of Claim 84 wherein the compound is of the general formula



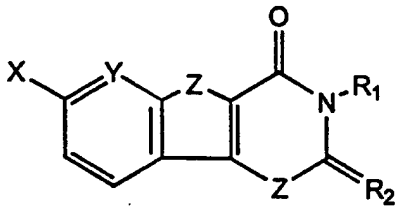
wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

100. The method of Claim 84 wherein the compound is of the general formula

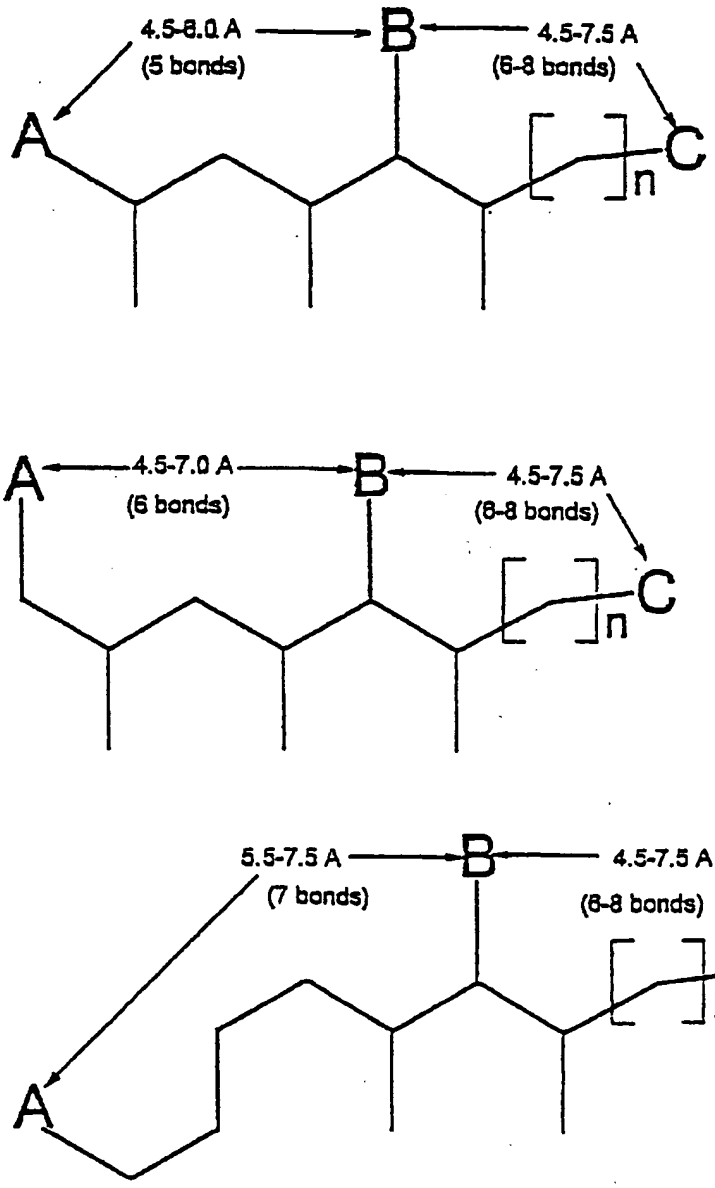


wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.

101. The method of Claim 84 wherein the compound is of the general formula



wherein X, Y, Z and R_1 have the meanings given for these variables in Claim 84 and R_2 is O, S, CH_2, or N-R_3, wherein R_3 is H, OH, alkyl and aryl.



A-C denote electronegative atoms

n = 3 - 5

Fig. 1

Examples of the electronegative atoms (A, B and C)

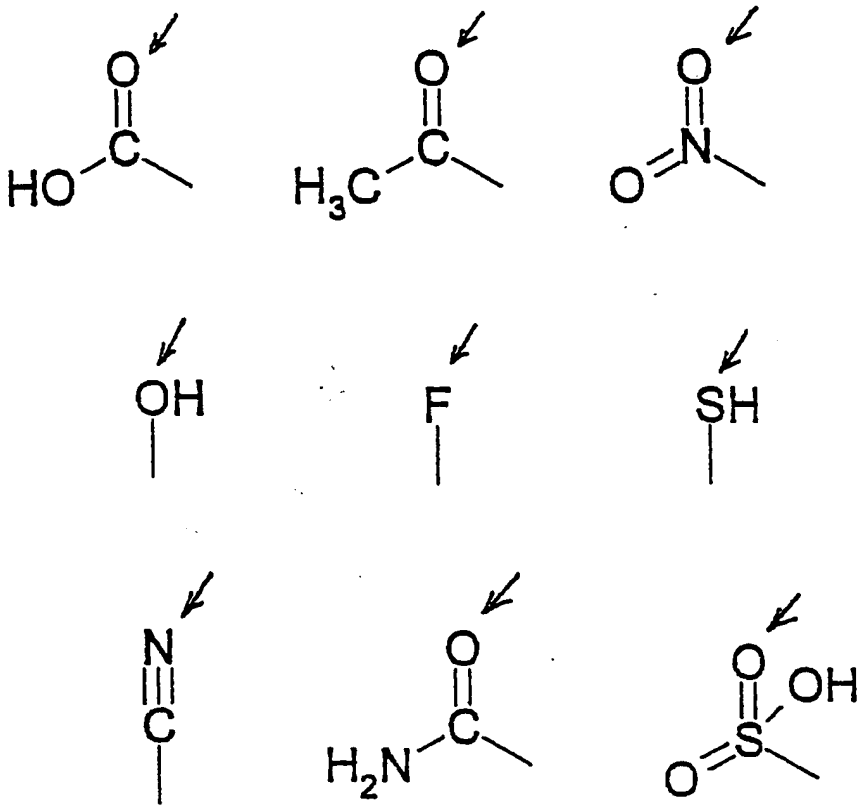


Fig. 2

Scheme1:

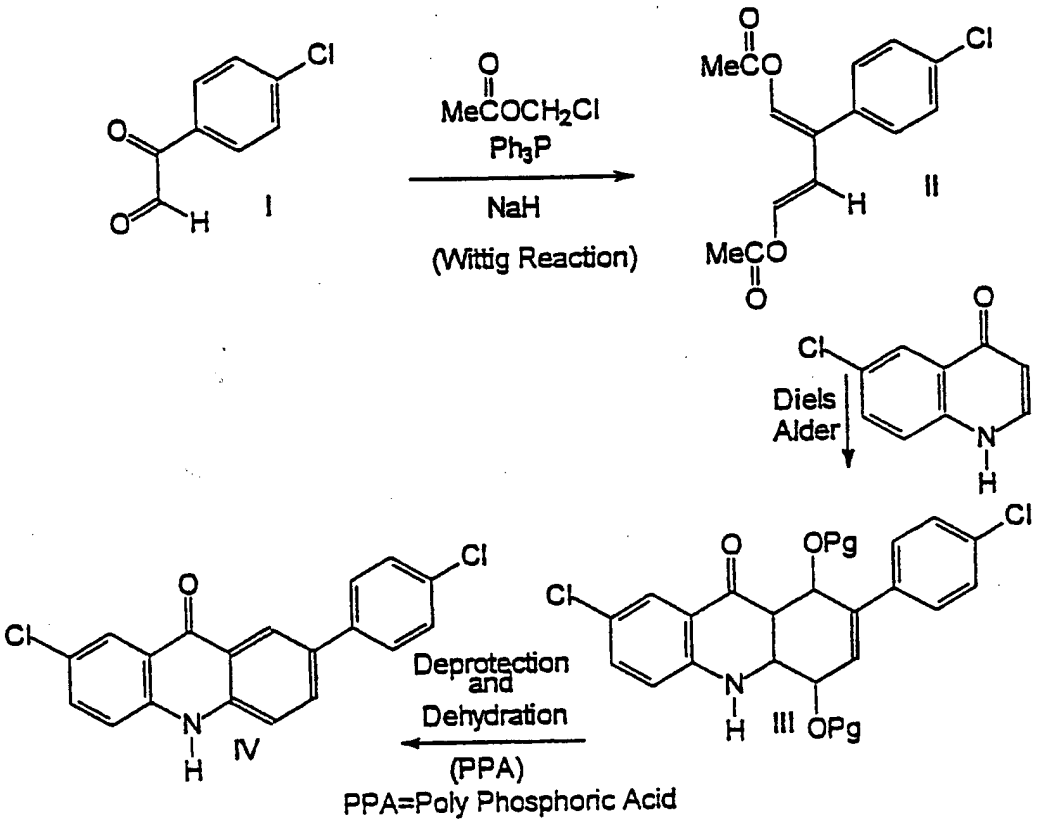


Fig. 3

Scheme 2:

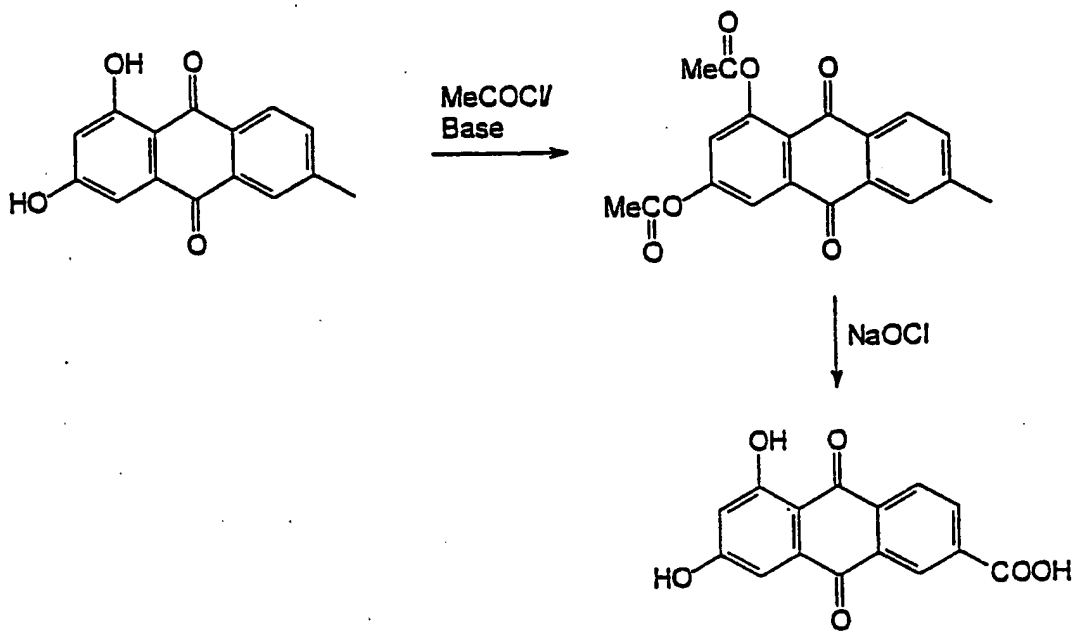


Fig. 4

Scheme 3:

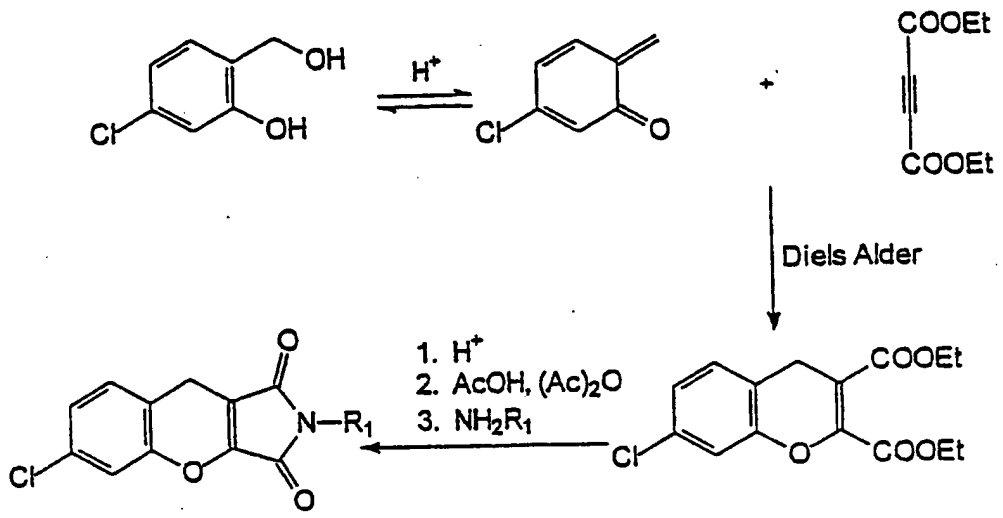


Fig. 5

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/CA 00/00542

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D221/14 A61K31/473 C07D209/48 A61K31/4035 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 17278 A (ALLELIX BIOPHARMA ;CHEN XIANNONG (CA); TEHIM ASHOK (CA)) 30 April 1998 (1998-04-30) claims	1-100
A	EP 0 206 322 A (I P A INTERNATIONAL PHARMACEUT) 30 December 1986 (1986-12-30) claims	1-100
A	US 3 821 383 A (SESTANJ K ET AL) 28 June 1974 (1974-06-28) claims	1-100
A	FR 2 521 139 A (KI I ENDOKRINOLOGII) 12 August 1983 (1983-08-12) claims	1-100

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2000	28/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/CA 00/00542

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 268 093 A (KNOLL AG) 25 May 1988 (1988-05-25) claims	1-100
A	WO 98 52919 A (JAPAN TOBACCO INC ;MIMURA TAKAYUKI (JP); SHINAGAWA YUKO (JP); KAWA) 26 November 1998 (1998-11-26) page 63 -page 118; claims	1-100
A	WO 98 34632 A (GSCHNEIDNER DAVID ;WANG ERIC (US); HO KOC KAN (US); LEIPOLD HARRY) 13 August 1998 (1998-08-13) claims	1-100
P,A	WO 00 00472 A (DU PONT PHARM CO) 6 January 2000 (2000-01-06) claims	1-100

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/CA 00/00542

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9817278 A	30-04-1998	AU 4696897 A	15-05-1998
		EP 0930883 A	28-07-1999
EP 0206322 A	30-12-1986	IT 1214618 B	18-01-1990
		AT 79755 T	15-09-1992
		DE 3686514 A	01-10-1992
		DE 3686514 T	11-02-1993
US 3821383 A	28-06-1974	NONE	
FR 2521139 A	12-08-1983	RU 2051677 C	10-01-1996
		JP 1491654 C	07-04-1989
		JP 58140072 A	19-08-1983
		JP 63035624 B	15-07-1988
EP 0268093 A	25-05-1988	DE 3635711 A	28-04-1988
		AT 76069 T	15-05-1992
		AU 592474 B	11-01-1990
		AU 7999087 A	28-04-1988
		CA 1331382 A	09-08-1994
		DE 3779053 D	17-06-1992
		ES 2037055 T	16-06-1993
		JP 63104963 A	10-05-1988
		US 5552544 A	03-09-1996
		ZA 8707859 A	28-06-1989
WO 9852919 A	26-11-1998	AU 7449198 A	11-12-1998
		JP 2921760 B	19-07-1999
		JP 11035559 A	09-02-1999
WO 9834632 A	13-08-1998	US 5776888 A	07-07-1998
		US 5804688 A	08-09-1998
		US 5876710 A	02-03-1999
		US 6060513 A	09-05-2000
		US 6051561 A	18-04-2000
		US 6090958 A	18-07-2000
		US 5939381 A	17-08-1999
		US 5990166 A	23-11-1999
		US 5773647 A	30-06-1998
		US 5879681 A	09-03-1999
		AU 6275698 A	26-08-1998
		EP 1015008 A	05-07-2000
		EP 0993831 A	19-04-2000
WO 0000472 A	06-01-2000	AU 4698299 A	17-01-2000